THE QUARTERLY JOURNAL OF MEDICINE

62F 3-109

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CRIGHTON BRAMWELL
W. D. W. BROOKS
A. M. COOKE
D. M. DUNLOP
H. L. MARRIOTT
ROBERT PLATT

NEW SERIES, VOLUME XIX
(VOLUME XLIII OF THE CONTINUOUS SERIES)
1950

1847 3

OXFORD
AT THE CLARENDON PRESS

Oxford University Press, Amen House, London E.C.4
GLASGOW NEW ORK TORONTO MELBOURNE WELLINGTON
BOMBAY CALCUTTA MADRAS CAPE TOWN
Geoffrey Cumberlege, Publisher to the University

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PRINTED IN GREAT BRITAIN
AT ' HE UNIVERSITY PRESS, OXFORD
BY CHARLES BATEY, PRINTER TO THE UNIVERSITY

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615.752.2:616.72–002.771

THE MODE OF ACTION OF SALICYLATE IN ACUTE RHEUMATIC FEVER[1]

By J. REID, R. D. WATSON, and D. H. SPROULL

(From the Clinical Chemotherapeutic Research Unit of the Medical Research Council in the Gardiner Institute of Medicine, University of Glasgow)

With Plate 1

Rheumatic fever has been recognized clinically for centuries, yet its cause is still uncertain, diagnosis often difficult, and treatment far from satisfactory (Stockman, 1920). Not only is the precise cause unknown, but also the reaction of the body to the disease is not fully understood. It therefore follows that little progress can be expected until more information on these fundamental points has been obtained. This position has long been recognized, but the difficulty has been to know how to begin an investigation that might provide the needed data. In considering the problem it seemed to us that the only notable landmark in the long history of the disease was the introduction of salicylate treatment by Buss (1875) and Maclagan (1876). Since then most clinical investigations have been principally concerned with the question of whether the drug cures rheumatic fever or merely relieves symptoms. This controversy has, unfortunately, obscured a reasonable line of approach to the fundamental problem, namely, the nature of the disease process in the acute rheumatic state. The relief of acute rheumatic manifestations such as fever, tachycardia, joint pain, and swelling with salicylate therapy is so dramatic and certain that if the exact mode of action of the drug on the body tissues were discovered, the harmful changes in the acute rheumatic state might be inferred and the hypothesis then put to the test of direct investigation. With the above points in mind, an attempt has been made to find out the mode of action of salicylate in rheumatic fever. All that is known at present is that acute rheumatic manifestations are promptly relieved and the erythrocyte sedimentation rate, when taken as an index of rheumatic activity, returns to normal provided a high plasma salicylate level is maintained (Coburn, 1943; Manchester, 1946; Reid, 1948). The connexion between the relief of symptoms and the fall in erythrocyte sedimentation rate is still obscure, but by discovering the link between them one important step might be taken in finding out the mechanism of how the drug acts in the body.

The present paper describes investigations which were carried out with this end in view, and two leads were provided by previous work (Reid, 1948). Firstly, relief of acute rheumatic manifestations was accompanied by a fall in the

[1] Received April 4, 1949.

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carbon dioxide combining power of the plasma, suggesting some association with alteration in the acid-base balance of the body fluids. Secondly, the fall in erythrocyte sedimentation rate was accompanied by a diuresis, implying that changes in volume of the body fluids were also involved. Our first problem therefore resolved itself into a study of the relation between acid-base changes and volume changes of the body fluids in patients with rheumatic fever during treatment with salicylate. Blood-plasma, one of the chief components of the body fluids, offered scope for direct investigation, the acid-base changes being assessed by estimation of plasma pH and plasma carbon dioxide content, and the plasma-volume being measured directly by intravenous injection of the dye T. 1824 (Gregersen and Stewart, 1939). Evidence, indirect but nevertheless reliable, of changes in total body-water and its distribution within the tissues was obtained by measurements of body-weight and urine volume, by studies of nitrogen balance, and by estimations of urinary sodium, chloride, and potassium. A fall in body-weight in association with a urine output in excess of the fluid intake was taken to be proof of a reduction in total body-water. A negative nitrogen balance indicating increased protein breakdown along with a urinary potassium output in excess of intake was accepted as evidence of a reduction in intracellular water. Finally, urinary sodium and chloride outputs greater than the intake of these ions implied diminution in volume of extracellular fluid. It was hoped by such tests on the blood-plasma and urine in rheumatic patients not only to detect major alterations in total body-water, but also to differentiate changes in the water content of the three chief sites of body-water, namely, cell protoplasm, interstitial spaces, and the blood-plasma itself.

Details of Procedure

A combined investigation of acid-base and water changes necessitated a large number of time-consuming tests on every patient studied, and required their co-operation. The investigations were, in fact, so extensive a labour that they were carried out fully in only four patients, but crucial tests were also repeated in three others. Adults were chosen, since the tests required complete co-operation and also because the acute manifestations of rheumatic fever relevant to our study are much more uniform in adults than in children. On admission to hospital the seven patients had fever, tachycardia, arthritis, and a raised erythrocyte sedimentation rate. All but one had received small doses of salicylate at home, but no salicylate was detected in the plasma of any on the morning after admission.

Diet. The patients were given a standard diet containing 50 to 60 gm. of protein, 200 to 275 gm. of carbohydrate, 45 to 55 gm. of fat, and 1·8 to 2·0 litres of fluid each day. The actual amount of food consumed and the fluid intake were carefully checked, and the daily protein, sodium, potassium, and chloride intakes calculated from tables (McCance and Widdowson, 1946).

Salicylate dosage. Five of the test patients were given 7·5 gm. of sodium salicylate by mouth daily in doses of 1·5 gm. at 6 a.m., 10 a.m., 2 p.m., 6 p.m.,

and 10 p.m. for 18 to 20 days unless the drug had to be stopped because of serious toxic effects. Sodium bicarbonate was purposely omitted to avoid difficulties in interpreting the results of the acid-base investigations. It is so customary, however, to give sodium bicarbonate along with sodium salicylate in the treatment of rheumatic fever that it seemed worth while to try to decide the possible importance of this practice by comparing the results of sodium salicylate therapy alone in the present investigations with those of combined sodium salicylate and sodium bicarbonate previously reported (Reid, 1948). As a check on the previous findings, two patients in the present series were therefore given 10 gm. of sodium salicylate and 10 gm. of sodium bicarbonate daily in 2 gm. doses at similar intervals to those of the other five patients. Plasma and urinary salicylate levels were estimated in all patients, and in four of the five who received sodium salicylate alone the amount of salicylate in the faeces was also determined, to obtain information on the rates of absorption, excretion, and degradation of the drug in the body.

Collection of samples. Blood specimens were taken at 10 a.m., immediately before the second daily dose of salicylate. The blood was collected directly from a vein into a paraffin-lined test-tube containing potassium oxalate, with the exception of the specimen for the determination of plasma pH and plasma carbon dioxide content, which was collected anaerobically under liquid paraffin to avoid alterations in pH and carbon dioxide content due to contact with air.

Methods. Salicylate was estimated in plasma, urine, and faeces by a double extraction method employing Jorrisen's colour reaction, which estimates both free and combined salicylate (Reid, 1948). A special technique was necessary for faeces. Water was added and a uniform suspension was prepared with a mechanical stirrer. The volume of the faecal suspension was measured and samples taken for salicylate estimation. The total amount of 'salicylate' in stools before and after the drug was given was never more than 0·05 gm., which is negligible in comparison with the total daily dose of 7·5 gm. given by mouth.

The erythrocyte sedimentation rate was determined in Westergren tubes set up immediately after collection of the blood.

Plasma pH was measured in a Cambridge potentiometer in a cell with calomel and glass electrodes.

Plasma carbon dioxide content was determined in a manometric Van Slyke apparatus.

Plasma-volume was estimated in every patient immediately before salicylate was given, at intervals of 5 to 10 days during its administration, and finally after it had been discontinued. A standard procedure was followed for each estimation. The patient was given 5 oz. of tea without milk and half a slice of dry toast at 8 a.m. At 9 a.m. a sample of blood for preparation of standards was collected in the manner described above. Fifteen mg. of the dye T. 1824 in 1·5 c.c. of water was then injected intravenously and four or five blood samples were taken at 15-minute intervals from other veins. The concentration of dye in each specimen was estimated with a Beckman spectrophotometer in comparison with standards prepared by adding a known amount of dye to samples of the plasma taken immediately before injection of the dye. The average plasma-volume was calculated by dividing the total quantity of dye injected by the average concentration of the dye in the plasma samples.

Total plasma-protein, plasma non-protein nitrogen, and urinary nitrogen

were estimated daily by the macro-Kjeldahl method. Urinary sodium, potassium, and chloride were likewise estimated every day by modifications of the pyroantimonate (Bálint, 1924), chloroplatinate (Hicks, 1913), and thiocyanate (Volhard, 1878) methods, respectively.

All tests except plasma-volume estimations were carried out daily in the four patients who received sodium salicylate alone. In the other three patients, urinary nitrogen, sodium, potassium, and chloride were not estimated, and the remaining tests were performed only when the plasma-volume was determined.

Results

The clinical effects of salicylate administration and the changes in erythrocyte sedimentation rate will first be described. The relation between the plasma level of the drug and the clinical effects will then be reported, followed by an account of the experiments on the absorption, excretion, and degradation of salicylate. Finally, the results of the plasma acid-base investigations and the body-water studies will be presented.

The clinical effects of salicylate administration. The clinical effects were the same in all seven patients. The well-known manifestations of the disease, namely, fever, tachycardia, joint pain, and swelling, disappeared within five days, but were replaced by a series of other clinical signs and symptoms which have attracted less attention, but seem to be of great scientific interest. During the initial five days the breathing changed, the rate became slower, and the depth gradually increased, until by the end of this period some patients were breathing as though they had air hunger. About the same time peripheral vasodilatation, slowing of the pulse-rate, progressive loss of appetite ending in nausea and vomiting, tinnitus, deafness, and a tendency to drowsiness also appeared. These symptoms and signs comprise a well-defined syndrome which for convenience of description will later be referred to as the 'special salicylate syndrome'. After the fifth day of full salicylate treatment the seven patients could be divided into two clinical groups. In the first group of four male patients the breathing became a little less deep, while nausea and vomiting disappeared and were replaced by an ever-increasing appetite. This last feature continued, until by the end of the second week all four patients felt hungry even after a meal, and apart from slight tinnitus and deafness and a tendency to over-sleep these were their only symptoms. In the second group of three patients, two female and one male, the breathing became still deeper, and nausea and vomiting persisted. Between the fifth and tenth days fever reappeared, drowsiness increased, mental confusion developed, and all three patients had dry tongues. Salicylate was immediately discontinued and the fluid intake much increased. On the following day the temperature began to fall and signs of dehydration were no longer present, but the mental symptoms cleared up more slowly and took about one week longer to disappear completely.

Two other clinical incidents are worth recording—severe epistaxis and pronounced slowing of the pulse-rate after withdrawal of sodium salicylate. The severe epistaxis developed in one female patient when she was fevered and severely dehydrated. It is known that haemorrhage from the nose and other

mucous membranes, although infrequent, does occur during salicylate treatment, and Link, Overman, Sullivan, Huebner, and Scheel (1943) have shown that salicylate causes prothrombin deficiency. The prothrombin index in our patient was therefore estimated (Quick, Stanley-Brown, and Barcroft, 1935) and found to be only 30 per cent. at the time of the haemorrhage. Synkavit (50 mg.) was injected intravenously to correct the prothrombin deficiency and dehydration was treated by giving sodium bicarbonate and encouraging the patient to drink water. On the following day the tongue was moist, the prothrombin index had risen to 55 per cent., and though slight epistaxis again

TABLE I

The Erythrocyte Sedimentation Rate and Salicylate Administration

	Initial value		*Value after 3 to 5 days' dosage*		*Value on last day of dosage*		*Final value*	
Case	*mm. in 1 hr.*	*day*	*mm. in 1 hr.*	*day*	*mm. in 1 hr.*	*day*	*mm. in 1 hr.*	*day*
1	125	1	117	4	83	9	48	16
2	118	1	104	5	76	11	35	31
3*	107	1	121	4	..	..	40	24
4	111	1	119	3	9	18	10	26
5	105	1	100	5	50	19	15	35
6*	81	1	117	4	85	17	66	24
7	60	1	108	4	70	18	..	..

* Cases 3 and 6 were given sodium bicarbonate and sodium salicylate; the others received sodium salicylate alone.

developed it lasted only for a few minutes and did not recur. Observations on this patient suggest that there may be two factors involved in haemorrhage during salicylate treatment: firstly, drying of the mucous membranes, which makes the blood-vessels more liable to rupture, and secondly, deficiency of prothrombin, which interferes with blood coagulation. The other clinical incident, a pronounced slowing of the pulse-rate from about 80 beats to between 40 and 50 per minute after withdrawal of the drug, was noted in all five patients who received sodium salicylate alone. This change suddenly developed 24 hours after the drug had been discontinued and persisted for about a week. Electrocardiograms showed that the bradycardia was of sinus origin.

The erythrocyte sedimentation rate and salicylate administration. The results in the seven patients, shown in Table I, ranged from 60 to 125 mm. in one hour immediately before salicylate administration. During the first five days of dosage high erythrocyte sedimentation rates showed little change while the lower values actually increased, so that at the end of this period the variation was only from 100 to 121 mm. in one hour. The erythrocyte sedimentation rates in all patients then began to fall, although at a variable rate, and the values on the last day of salicylate administration ranged from 9 to 85 mm. in one hour. The final figures, three to five weeks from the start of treatment, were 10 to 66 mm. in one hour.

The relationship between plasma salicylate levels and clinical changes. While the acute rheumatic manifestations were being relieved and hyperpnoea, slowing

of the pulse-rate, peripheral vasodilatation, nausea, vomiting, tinnitus, deafness, and drowsiness were developing, the plasma salicylate level was progressively rising. The more rapid the rise, the quicker was the relief of acute rheumatic symptoms and the more severe the signs and symptoms of the 'special salicylate syndrome'; the clinical effects of the drug thus seemed to be directly related to the plasma salicylate level. The relationship between plasma salicylate levels and the 'special salicylate syndrome' was particularly clear on the tenth day of treatment when, as has already been stated, the development of fever and serious dehydration in some patients separated our cases into two clinical groups. Symptoms in one group of four patients had at this time become less severe, and the plasma salicylate levels ranged from 30 to 38 mg. per 100 c.c. Symptoms in the other group of three patients had, on the other hand, become more intense, and the plasma salicylates in two were 65 and 72 mg. per 100 c.c. The level in the third patient was not estimated, but the high urinary excretion of the drug indicated that the plasma value must also have been high, since the plasma and urinary salicylate levels tend to run parallel. These findings support the clinical observation that the depth of the breathing and other signs of the 'special salicylate syndrome' are directly related to the plasma level of the drug.

Urinary and faecal salicylate. The total amount of salicylate excreted in the urine and faeces of four patients who received sodium salicylate alone was estimated throughout the whole period of therapy in order to obtain information on the absorption, excretion, and degradation of the drug after prolonged administration. The completeness of absorption from the gastro-intestinal tract was assessed by comparing the total oral dose with the amount of salicylate recovered from the faeces. The total excretion was calculated by adding together faecal and urinary salicylates, as Hanzlik, Scott, and Thoburn (1917) have shown that the loss in sweat, the other possible route of excretion, is insignificant. Finally, the extent of degradation of salicylate in the body was estimated by calculation. The total dose and the total amount of the drug excreted were known, so that the difference between them represents the quantity of drug that has disappeared and can be accounted for only by degradation within the body. It is evident from the results of the urinary and faecal salicylate estimations shown in Table II that only a comparatively small portion of the total dose was recovered from the stools. This was not due to a fault in the method, since it was possible to recover salicylate quantitatively after its addition to the faeces of each patient, even after incubation at 37° C. for five days. Further, it was not due to combination of the drug with other compounds, as boiling the faeces with dilute hydrochloric acid and taking precautions to avoid loss of salicylic acid by evaporation never increased the yield. It was therefore concluded that only small quantities of the drug were actually present in the faeces of our patients. The total amount in the four patients ranged from 1·2 to 2·0 gm., which is insignificant in comparison with a total dosage of 60 to 147 gm. Absorption must therefore have been almost complete unless the drug was destroyed in the bowel, but this is most unlikely, as the

incubation experiments with known quantities of salicylate in faeces appear to show.

The total urinary salicylate, though greater than the faecal salicylate, was still far short of the total dose, and only 20 to 30 per cent. of the amount given was excreted in the urine. Even when the figures of faecal salicylate were added to the urinary salicylate only 22 to 32 per cent. of the total dose could be

TABLE II

Urinary and Faecal Salicylate in relation to Dose

		Total urinary salicylate		*Total faecal salicylate*	
Case	*Total dose gm.*	*gm.*	*Percentage of dose*	*gm.*	*Percentage of dose*
1	60	12·2	20·3	1·2	2·0
4	135	41·5	30·7	2·0	1·5
7	135	34·5	25·5	1·2	0·9
5	147	35·9	24·4	2·0	1·3

TABLE III

Plasma pH and Salicylate Administration

Case	*Value before salicylate administration*	*Peak value during salicylate administration*	*Values 3 to 6 days after salicylate administration*
5	7·62	7·75	7·49
4	7·61	7·74	7·54
1	7·59	7·73	7·42
7	7·58	7·62	7·50
2	7·50	7·58	7·57
3*	7·50	7·58	7·42
6*	7·50	7·60	7·49
Average	7·56	7·66	7·49

* Cases 3 and 6 were given sodium bicarbonate along with sodium salicylate; the others were given sodium salicylate alone.

accounted for. This meant that 68 to 78 per cent. of the drug had apparently disappeared, and was presumably converted into other compounds within the body. The results thus confirm the short-term studies of Hanzlik, Scott, and Thoburn (1917) and indicate that even after prolonged oral salicylate administration absorption is for all practical purposes complete, and that a considerable quantity of the drug is degraded within the body.

Acid-base changes in plasma. Alterations in the acid-base composition of plasma were assessed by plasma pH determinations in all seven patients, and by simultaneous estimation of the plasma carbon dioxide in four patients who received sodium salicylate alone. By this combination of two tests the possibility of finding out the precise cause of any alteration was enhanced, since plasma pH ultimately depends on the relative amount of carbonic acid and sodium bicarbonate present. The seven patients showed a similar trend of changes in plasma pH, but in varying degree (Table III). The pH invariably increased after salicylate administration from initial values of 7·50 to 7·62 to peak values of 7·58 to 7·75 during the first 10 days of dosage. The rise tended

to be more pronounced in the patients who received sodium salicylate alone than in the two patients who in addition also received sodium bicarbonate. After peak values were reached the plasma pH figures began to fall slowly for the remaining period that salicylate was given. Withdrawal of the drug immediately resulted in a sharp fall to much lower values (7·42 to 7·57) and this was followed again by a rise to the values observed before the drug was given. These

TABLE IV

Plasma Carbon Dioxide Content and Salicylate

Case	*Initial plasma CO_2 (vols. per 100 c.c.)*	*Plasma CO_2 after 7 days' treatment with salicylate (vols. per 100 c.c.)*	*Plasma CO_2 3 to 6 days after salicylate administration (vols. per 100 c.c.)*
4	54·5	37·0	55·5
7	52·5	39·0	56·0
5	50·0	33·5	49·0
1	48·0	25·0	49·0
Average	51·2	33·6	52·4

All four patients received sodium salicylate alone.

results indicate that patients with acute rheumatic fever tend to have an alkalosis before salicylate is given, which is intensified by administration of the drug. The plasma carbon dioxide content of the four patients who received sodium salicylate alone ranged from 48·0 to 54·5 vols. per 100 c.c. immediately before treatment started, and then progressively fell to 25 to 39 vols. per 100 c.c. at the end of the first week. Thereafter the plasma carbon dioxide content of the patients differed. Three patients belonged to the group of four in whom hyperpnoea and the other symptoms of the 'special salicylate syndrome' subsided, while the other patient was one of the three whose symptoms became more intense in association with signs of severe dehydration. The plasma carbon dioxide content of three patients actually increased while hyperpnoea and other symptoms were abating, while that of the other patient progressively fell to the very low value of 12 vols. per 100 c.c. on the day that symptoms and dehydration were most pronounced. The severity of the signs and symptoms of the 'special salicylate syndrome' thus appeared to be inversely related to the plasma carbon dioxide content: the lower the plasma carbon dioxide the more severe were the symptoms, and vice versa. After salicylate treatment the plasma carbon dioxide content of all patients rapidly rose in the course of the next few days to 49 to 56 vols. per 100 c.c. (Table IV). The findings thus suggest that the general effect of salicylate treatment is to lower the plasma carbon dioxide content.

Correlation of the changes in plasma pH and carbon dioxide content in association with salicylate administration brings out some curious points. Increase in plasma pH accompanied by a fall in carbon dioxide content shows that carbon dioxide is removed from the plasma by the lungs much more rapidly than fixed-base is excreted by the kidneys. The result is that the H_2CO_3: $NaHCO_3$ ratio is diminished, and plasma pH therefore rises. In other words,

salicylate appears to induce a respiratory alkalosis, and the deep breathing in our patients after the administration of the drug would explain this observation. Furthermore, the inverse relationship between the plasma salicylate level and the carbon dioxide combining power (Reid, 1948) has now been found to hold

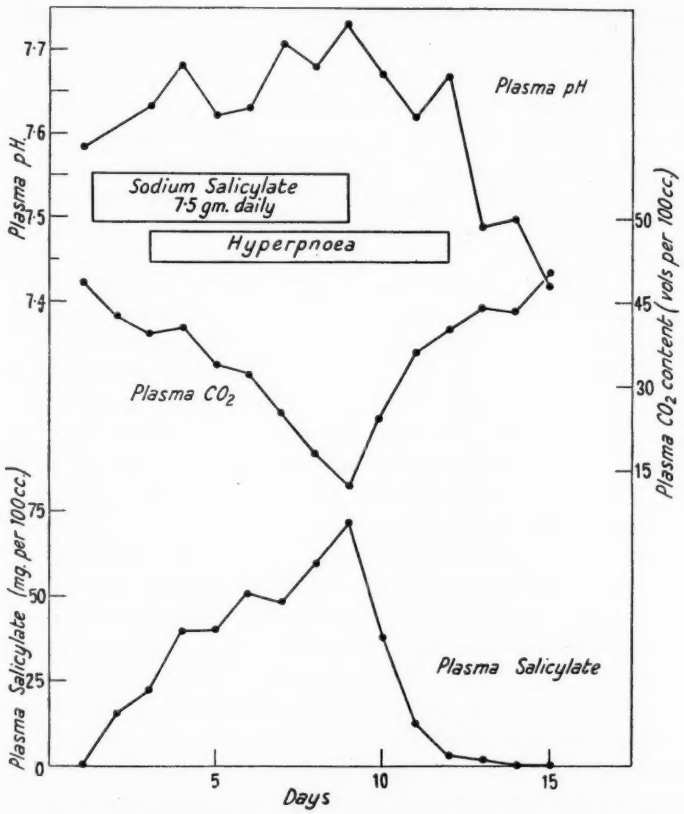

FIG. 1. The relationship between the plasma salicylate level, plasma carbon dioxide content, and plasma pH. As the plasma salicylate rises, the carbon dioxide content falls and plasma pH increases, and conversely, as the plasma salicylate falls the carbon dioxide content rises and the pH falls.

also for the plasma carbon dioxide content, so that the clinical observation that the depth of breathing is proportional to the plasma salicylate level is substantiated. These points are illustrated in Fig. 1, where the relation between plasma pH, carbon dioxide content, and salicylate levels are shown. In a previous paper (Reid, 1948) it was suggested that salicylate induced an acidosis. This is obviously incorrect. The error arose from misinterpretation of observations on carbon dioxide combining power and urinary pH, and chiefly because the possibility of a respiratory alkalosis was not considered.

Changes in total plasma-volume. The changes in plasma-volume resulting from salicylate administration are also striking. The plasma-volume of the seven acutely ill patients just before salicylate was given ranged from 3·3 to 5·0 litres, the values being greater than would have been expected from the weights of the patients. Much lower values were recorded when the patients had either improved or had recovered completely, which suggest that an increased plasma-volume is an important abnormality in the acute rheumatic state when fever, tachycardia, and arthritis are present. The results are shown in Table V. During the first two weeks of therapy the plasma-volume of the four patients who escaped serious dehydration rose sharply to 4·4 to 5·5 litres, and then fell. On the other hand, three patients who suffered from severe dehydration had fairly high initial plasma-volumes which fell more or less progressively from the start of therapy. The general effect of salicylate, if dehydration is avoided, therefore seems to be to induce an initial sharp rise in plasma-volume followed by a more gradual fall. Similar changes in the plasma-volume of six patients with rheumatic fever during salicylate treatment have already been reported by York and Fischer (1947), though in only one of their patients was a pronounced increase noted. A high initial plasma-volume during the early stage of rheumatic fever may, when accentuated by salicylate therapy, have serious consequences in children. This has been shown in our observations on two girls of 13 and 15 years who developed rheumatic fever, which was treated with salicylate. Pain, fever, and tachycardia were quickly relieved, but between the sixth and tenth days of therapy both developed extensive bilateral pulmonary oedema with dullness and tubular breathing at the lung bases. At this time the total plasma-volumes were 2·5 and 3·6 litres, but four to six weeks later the values had fallen to 1·8 and 2·7 litres respectively, and the fall was accompanied by marked clinical improvement. The extent of the lesion and the amazing recovery in the younger patient are illustrated by X-ray photographs in Plate 1, Fig. 4. The symptoms, signs, and X-ray appearances noted in both children seem identical with those of so-called rheumatic pneumonia. They suggest that the basis of this condition may simply be pulmonary oedema precipitated by an increase in plasma-volume in a patient with an already damaged heart. In attempting to explain the changes in plasma-volume described above, the protein and mineral content of plasma must be considered, and these will now be dealt with in turn. For convenience, nitrogen balance studies will be described along with the estimations of plasma protein.

Plasma-protein and nitrogen balance estimations. The plasma-proteins of the seven patients immediately before salicylate dosage ranged from 6·83 to 8·20 gm. per 100 c.c. and averaged 7·37 gm. per 100 c.c. (Table V). There was no uniform change during the first five days, but by the twelfth day of therapy the figures in all patients had fallen appreciably; the fall continued until the seventh to ninth day after withdrawal of the drug, when the range was 5·6 to 7·0 gm. per 100 c.c. and the average value 6·2 gm. per 100 c.c.

It is shown in Table V that while the average plasma-protein content fell after the twelfth day, the average plasma-volume remained practically un-

changed during the whole period of salicylate therapy. This suggests that the fall in plasma-protein is real, and not simply a dilution effect. The total plasma-protein, calculated from the observed concentration and the plasma-volume, confirmed this, as it was greatly reduced in every patient. The initial values ranged from 261 to 394 gm. of protein and averaged 304 gm.; the values seven to nine days after treatment ranged from 190 to 279 gm. and averaged

TABLE V

Plasma-volume, Plasma-protein, and Salicylate Therapy

	Immediately before salicylate administration		*During salicylate administration*						*After salicylate dosage*					
			4th to 5th day		*9th to 12th day*		*16th to 20th day*		*7th to 9th day*		*14th day*		*20th day*	
Case	*Plasma-volume (litres)*	*Plasma-protein (gm. per 100 c.c.)*	*Plasma-volume (litres)*	*Plasma-protein (gm. per 100 c.c.)*	*Plasma-volume (litres)*	*Plasma-protein (gm. per 100 c.c.)*	*Plasma-volume (litres)*	*Plasma-protein (gm. per 100 c.c.)*	*Plasma-volume (litres)*	*Plasma-protein (gm. per 100 c.c.)*	*Plasma-volume (litres)*	*Plasma-protein (gm. per 100 c.c.)*	*Plasma-volume (litres)*	*Plasma-protein (gm. per 100 c.c.)*
3	5·0	7·45	4·8	7·50	..	..	..	..	4·5	5·70	3·4	7·10	2·8	7·10
7	4·8	8·20	4·1	7·94	5·4	7·66	4·2	6·53	4·1	6·81	..	..	..	..
4	4·2	6·78	5·3	6·81	4·0	5·89	4·4	5·57	3·3	5·92	..	..	..	..
1	4·0	6·83	3·2	7·46	3·7	6·78	..	..	3·2	6·38	3·4	7·09	3·1	6·61
2	4·0	7·06	3·6	7·18	3·2	6·43	..	..	3·4	5·60	..	..	3·0	6·90
5	3·6	7·27	4·1	7·48	5·5	7·0	4·1	6·27	3·6	6·0	2·8	8·10	..	..
6	3·3	7·90	4·4	6·80	4·3	6·60	3·8	7·04	3·1	7·0	..	..	..	..
Average	4·1	7·37	4·2	7·31	4·3	6·72	4·1	6·35	3·6	6·20	..	..	..	..

Cases 1, 2, and 3 became so severely dehydrated that salicylate administration had to be discontinued.

222 gm., so that the average reduction was about 82 gm. of protein. Observations on plasma non-protein nitrogen and nitrogen balance studies in the four patients who were given sodium salicylate alone, fit in with the changes in the plasma-protein just described. The effect of giving salicylate was to keep the patients in negative nitrogen balance during the whole period the drug was given. The difference between nitrogen output in urine and faeces and the dietary intake was greatest in the first week and became progressively less during the remaining period of salicylate administration. After the drug was discontinued the position was reversed and for a few days intake of nitrogen was greater than output (Fig. 2). While salicylate was being given the total loss of nitrogen was greater than that entailed in the fall in plasma-protein, so that cellular nitrogen must also have been diminished. This implies that the protein content of cells as well as of plasma was reduced by the action of the drug. An unexpected parallelism was observed in three of the four patients during treatment, in that changes in nitrogen balance mirrored fairly accurately the changes in plasma-protein (Fig. 2). Moreover, though this relationship seemed at first absent in the remaining patient it was masked only by the fact that the non-protein nitrogen was accumulating in the blood instead of being excreted in the urine. This was probably the result of a temporary disturbance of renal function. These observations indicate that equilibrium between circulating plasma-protein and cellular protein, postulated as a basic physiological

principle by Madden and Whipple (1940), is maintained even while total body protein is being reduced. A rise in plasma non-protein nitrogen, though not so pronounced or sustained as that noted in the patient just referred to, was also observed in the remaining three patients, particularly during the first 10 days

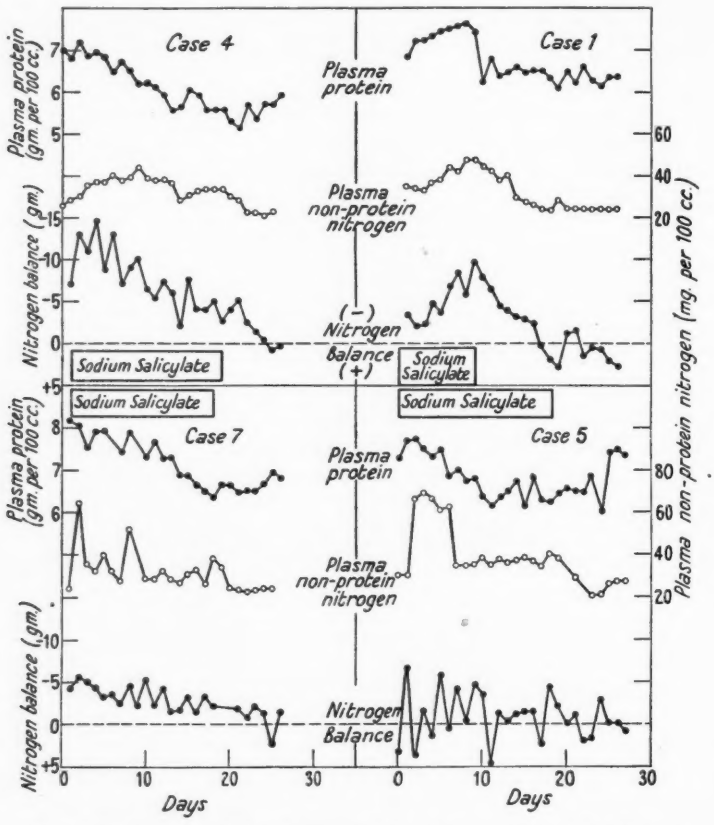

FIG. 2. The results of the plasma-protein, plasma non-protein nitrogen, and nitrogen balance studies in the four patients with rheumatic fever who were given sodium salicylate alone. All were in negative nitrogen balance throughout the period of salicylate administration, and during this time the changes in plasma protein tended to follow the nitrogen balances in Cases 1, 4, and 7. In the remaining patient (Case 5) this relationship was masked by the development of a mild azotaemia.

of treatment. Withdrawal of the drug was invariably associated with a significant fall in plasma non-protein nitrogen, so that salicylate, in addition to stimulating protein k. tabolism, appears also to increase plasma non-protein nitrogen. The next step in the investigation was to find out the general effect of these changes in protein metabolism on total body-water, and in particular on the distribution of water in the body, that is, in the interstitial spaces and actual cell protoplasm.

Total body-water. Gross changes in total body-water were assessed by measurements of the body-weight, urine volume, and fluid intake. With these tests it was possible to be definite only about a reduction in total body-water as it was not practicable to measure water loss by other routes such as respiration and sweating. Diminution in total body-water was indicated by a fall in weight associated with a urine volume in excess of the fluid intake. The body-weights

TABLE VI

Body-weight and Salicylate Therapy

Case	*Weight before salicylate administration* (*kg.*)	*Weight on last day of salicylate administration* (*kg.*)	*Weight 7 to 14 days after salicylate administration* (*kg.*)	*Total reduction in weight* (*kg.*)
7	55·4	53·2	53·0	2·4
4	56·2	55·5	52·0	4·2
5	71·0	67·8	67·0	4·0
2	73·4	..	68·4	5·0

of the four patients on whom observations were made all fell by amounts varying from 2·4 to 5·0 kg. The results before salicylate administration, at the end of treatment, and seven to 14 days later, are shown in Table VI. The fall in weight started while salicylate was being given and continued after the drug had been withdrawn. It was associated during the period of salicylate therapy with a progressive rise in urine volume that culminated in a real diuresis immediately after the drug had been stopped. The fall in weight therefore seems to be associated with a diminution in total body-water. The delay in the occurrence of diuresis until after the drug was withdrawn was a constant feature in patients treated with sodium salicylate alone. It contrasted with an earlier diuresis which developed during the period of therapy in the two patients who were given sodium bicarbonate along with sodium salicylate, and also in a previous group of patients who were given both drugs (Reid, 1948). It therefore seems that administration of sodium bicarbonate has an important bearing on the time of onset of the diuresis.

Extracellular water. Changes in the volume of extracellular water, which includes interstitial and plasma water, have been assessed by comparing urinary sodium and chloride excretion with the dietary sodium and chloride intake. Like the observations on total body-water this method has only a limited value in that it is only when the urinary output of both ions exceeds intake that the volume of extracellular water is reduced. The estimations were again confined to the four patients who were given sodium salicylate alone. Remarkably close agreement in the results were obtained in all four patients (Fig. 3). Changes in total urinary chloride mirrored the changes in total urinary sodium, and both reflected accurately the variation in urine volume. The urinary output of both ions was much less than the intake in all patients from the second day of treatment until the drug was withdrawn. Immediately after dosage was suspended the output of sodium and chloride exceeded the intake, thus indicating that

the volume of extracellular fluid was reduced after administration of the drug had been stopped. The association of excessive urinary sodium and chloride outputs with a diuresis in the post-salicylate period confirms this deduction.

Intracellular or protoplasmic water. As the volume of water in cells is mainly dependent on their content of protein and mineral salts, it follows that gross

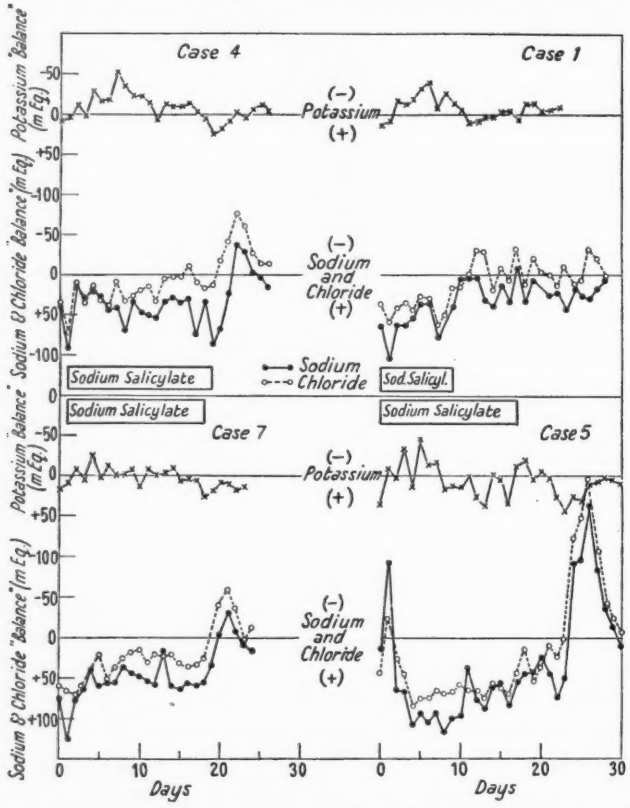

FIG. 3. The difference between the urinary output and the dietary intake of potassium, sodium, and chloride in the four patients with rheumatic fever who were treated with sodium salicylate. The general trend of the results was the same in all four patients. The urinary output of potassium exceeded the dietary intake in the early days of salicylate administration, while the urinary output of sodium and chloride exceeded the intakes immediately after withdrawal of the drug.

alterations in cellular water may be inferred if the general changes in these two constituents are known. Protein changes have been assessed by nitrogen balances and mineral changes by comparing urinary potassium output with potassium intake in the same four patients who were given sodium salicylate alone. Potassium was selected for estimation because it is the predominant intracellular ion. It has already been shown that during the administration of salicylate all four patients were in negative nitrogen balance. The excess of

urinary nitrogen over dietary nitrogen was most pronounced in the early days of salicylate dosage, and was greater than could be accounted for by the reduction in total plasma-protein, so that cellular protein must also have been reduced. Furthermore, as the urinary potassium exceeded the intake during the same period (Fig. 3), it was concluded that a diminution in intracellular water was an important early effect of salicylate treatment.

Discussion

Our aim has been to find out how salicylate acts in rheumatic fever, by looking for a connexion between the analgesic action of the drug and its effect on the erythrocyte sedimentation rate. This unusual approach to the problem was the logical sequel to a previous study (Reid, 1948) and necessitated simultaneous investigation of reaction changes and volume changes in the body fluids of a limited number of patients with acute rheumatic fever during salicylate treatment. Consistent results were obtained in each of the seven patients studied, so that there is no doubt about the accuracy of the findings. It seems necessary, however, to bring together again the main clinical and biochemical changes which follow salicylate administration before discussing their interrelations and possible significance.

Fever, tachycardia, joint pain, and swelling are completely relieved in the first five days of salicylate therapy, and during this time a well-defined syndrome also appears, the clinical manifestations of which are hyperpnoea, slowing of the pulse-rate, peripheral vasodilatation, nausea, vomiting, tinnitus, deafness, and drowsiness. As acute rheumatic manifestations recede, the 'special salicylate syndrome' develops until by the fifth day all the symptoms and signs are usually well established. They then tend to subside in some patients, but become more severe in others and eventually lead to severe dehydration, fever, mental disturbances, and drowsiness. Subsidence of the symptoms of the special syndrome is associated with a falling plasma salicylate level; aggravation of symptoms, on the other hand, is associated with a continuously rising plasma salicylate level that reaches very high levels. The severity of the 'special salicylate syndrome', like the promptness of relief of fever, tachycardia, joint pain, and swelling, is thus related to the plasma salicylate level; the higher this level the more intense the special syndrome and the quicker the relief from the ordinary well-recognized features of acute rheumatism. The deepening of the breathing, constantly observed, has an important effect on the reaction of the plasma. An accentuation of the alkalosis that exists before salicylate treatment results from the administration of the drug. This is due to an excessive loss of carbon dioxide by deep breathing which is not fully compensated by renal excretion of fixed base.

The accompanying changes in the three main reservoirs of body-water are equally striking. The general effect of salicylate is to reduce the volume of total body-water, but the water loss from cells, interstitial spaces, and plasma is not uniform. Cellular water is the first to be reduced and is later followed by a similar reduction in the water content of the other two compartments. The

principal factor responsible for these changes is a diminution in body protein as indicated by the negative nitrogen balances. These studies, in conjunction with the plasma-protein and plasma-volume estimations, suggest that both cellular and total plasma-protein are reduced as a result of salicylate administration. The changes in body-water are not surprising in so far as the proteins are mainly responsible for the amount of water which is held in the body. What is surprising, however, is the remarkable similarity in the events accompanying the relief of joint pain and swelling on the one hand, and a fall in erythrocyte sedimentation rate on the other. Joint pain and swelling are relieved simultaneously, and while this is happening the protein, potassium, and water content of the body cells are being reduced. The erythrocyte sedimentation rate shows no sign of falling at this stage, but when the protein, sodium chloride, and water content of the plasma later begin to fall, so also does the erythrocyte sedimentation rate. This striking correlation between the events associated with the relief of joint pain and swelling and a fall in the erythrocyte sedimentation rate suggests, firstly, that the choice of the erythrocyte sedimentation rate as an index of rheumatic activity is essentially sound, and secondly, that cure of an attack of rheumatic fever with salicylate is a double process. In the first stage, joint pain and swelling are relieved by transfer of water from the affected joint tissues to the extracellular fluid; in the second, the erythrocyte sedimentation rate returns to normal when the excess water is removed from the body, mainly by diuresis. The successful treatment of rheumatic fever will on this view depend on the smooth integration of these two processes.

It is clear from the results described that salicylate has two important pharmacological actions: (1) the stimulation of protein katabolism, which has been shown to be ultimately responsible for the analgesic action of the drug and for the return of the erythrocyte sedimentation rate to normal, and (2) the induction of a respiratory alkalosis by deep breathing. Although it is not possible with the data available to be certain which is primary, recent experimental work by Graham and Parker (1948) suggests a possible explanation of how these effects arise. These authors have shown that hyperpnoea resulting from intravenous injection of sodium salicylate in experimental animals is completely inhibited by section of both vagi. This important observation indicates that salicylate acts on vagal nerve-endings; and a similar action in man is shown to be more than probable, firstly, because deep breathing in experimental animals causes a respiratory alkalosis just as it does in man (Boyle, Smull, and Wégria, 1947), and secondly, because many of the signs and symptoms of the 'special salicylate syndrome' such as hyperpnoea, slowing of the pulse-rate, peripheral vasodilatation, nausea, and vomiting are explainable on the basis of stimulation of the vagus nerves. It is thus possible that the primary pharmacological action of salicylate is to stimulate vagal nerve-endings and induce a respiratory alkalosis by deep breathing, which, as a secondary effect, leads to increased protein katabolism by altering the chemical environment of body cells. Alternatively, stimulation of protein katabolism may be the primary action, and this may lead to vagal excitation by liberating nitrogenous organic compounds from

the breakdown of protein. The problem will require further investigation before the primary action of salicylate is finally decided.

It may now be asked how the therapeutic action of salicylate fits in with the well-known natural tendency for an acute attack of rheumatic fever to cure itself. Our evidence suggests that the therapeutic action of salicylate differs in no way from the natural mechanism, since the biochemical changes in acute untreated rheumatic fever are simply exaggerated by the administration of the drug. For example, the existing alkalosis becomes more severe and the plasma-volume tends to rise farther while joint pain and swelling are subsiding. These facts suggest that salicylate does little more than speed up and possibly intensify the natural curative process. One final question arises, namely, how do the findings in the present investigation affect our outlook on the treatment of rheumatic fever with salicylate? The belief has been widely held that salicylate does little more than act as an anodyne. The evidence presented in the present paper seems to refute this view and suggests what salicylate actually does in the cure of an attack of rheumatic fever. The fact that relapses may immediately follow withdrawal of the drug implies, as suggested by Coburn (1943), that salicylate cures only existing acute rheumatic lesions and prevents the development of new ones, though it does not eradicate the cause. The therapeutic action of salicylate in rheumatic fever may thus in a general sense be compared with that of liver extracts in pernicious anaemia, since both medicaments correct and prevent pathological changes without removing the primary cause. Salicylate, although it undoubtedly has curative properties, also has drawbacks. Two factors are responsible for these: firstly, the therapeutic plasma level of the drug is very close to the toxic level, and secondly, the plasma salicylate levels of patients who receive the same dose of the drug vary greatly. It is therefore very difficult to recommend therapeutic doses of salicylate that will be effective in every patient, so that it is still advisable to control dosage by plasma or urinary salicylate estimations to ensure that the greatest possible advantage is obtained from the drug. It might be possible to control dosage clinically by careful observation of the breathing, since depth of respiration is found to be proportional to the plasma salicylate level. However, if complete reliance is placed on clinical observation a close watch must be kept for early signs of dehydration which, in conjunction with very deep breathing and the recurrence of fever, will indicate that the plasma salicylate level is becoming dangerously high. Another serious though less frequent development that must also be kept in mind is pulmonary oedema, which is probably due to left ventricular failure after a temporary rise in plasma-volume. This rise in plasma-volume, when pronounced, is associated with a fall in the level of plasma salicylate, so that the two major complications of salicylate treatment, the onset of dehydration and pulmonary oedema, are indicative of rising and falling plasma salicylate levels respectively. Fortunately, dehydration quickly responds to oral administration of sodium bicarbonate and water. The treatment of pulmonary oedema is not so satisfactory, though immediate benefit is obtained from venesection.

A problem that always confronts the physician is how long to continue dosage. This question has never been satisfactorily answered, though there are now good reasons for persisting with the drug until the erythrocyte sedimentation rate returns to normal. Moreover, as our observations indicate that a fall in the erythrocyte sedimentation rate is associated with a diuresis if sodium bicarbonate is given along with sodium salicylate, it might be possible to decide the duration of dosage by continuing both drugs until a diuresis develops. It will be evident from these observations that the treatment of rheumatic fever does not begin and end with the administration of salicylate. General principles for the clinical control of treatment have been outlined, but it will nevertheless be found helpful to supplement clinical observation by estimating the plasma salicylate level if the serious consequences that may attend the use of the drug in fully effective doses are to be anticipated, and so avoided.

Summary

1. The introduction of salicylate for the treatment of rheumatic fever is still considered to be the most important event in the long history of the disease. The effect of the drug on acute rheumatic manifestations is so striking that if its exact mode of action were discovered the nature of the disease process in the acute rheumatic state might be inferred.

2. An attempt to define the mode of action of the drug has been made by investigating simultaneously factors that may be responsible for the relief of acute rheumatic manifestations and the return of the erythrocyte sedimentation rate to normal. This has involved observations on the acid-base and volume changes of internal body fluids in seven adult patients with rheumatic fever while they were being treated with salicylate.

3. The principal pharmacological actions of the drug are to stimulate protein katabolism and aggravate a respiratory alkalosis. These changes not only relieve the well-known manifestations of acute rheumatic fever, but are also responsible for a special clinical syndrome.

4. The principal symptoms and signs of this syndrome are hyperpnoea, slowing of the pulse-rate, peripheral vasodilatation, nausea, vomiting, tinnitus, deafness, and drowsiness. These symptoms appear while acute rheumatic manifestations are being relieved, and the promptness of relief of rheumatic symptoms and the severity of the special syndrome are both directly related to the plasma salicylate level; the higher this level the quicker the disappearance of fever, tachycardia, joint pain and swelling, and the more intense the symptoms of the added salicylate syndrome.

5. As a result of the increased protein breakdown the distribution of water within the body is profoundly altered. The first change is a reduction in cellular water, which is associated with a temporary increase in plasma and interstitial fluid volumes, and is later followed by a diminution in both, as indicated by a fall in plasma-volume and by the development of a diuresis.

6. The relief of joint pain and swelling and a fall in the erythrocyte sedimentation rate are both associated with the removal of water from cells and plasma

respectively. This dehydrating effect follows a reduction in cellular and plasma-protein which results from increased protein katabolism. The implications of these findings and their influence on treatment of rheumatic fever with salicylate are discussed.

We wish to thank Professor J. W. McNee for helpful criticism, Miss M. G. McCombie, Miss M. C. MacKintosh, and Miss H. M. Nodwell for preparation and careful supervision of the diets, Mr. A. Sinclair and Mr. D. Williamson for technical assistance, and Miss N. Elder for preparation of the manuscript.

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FIG. 4*a*

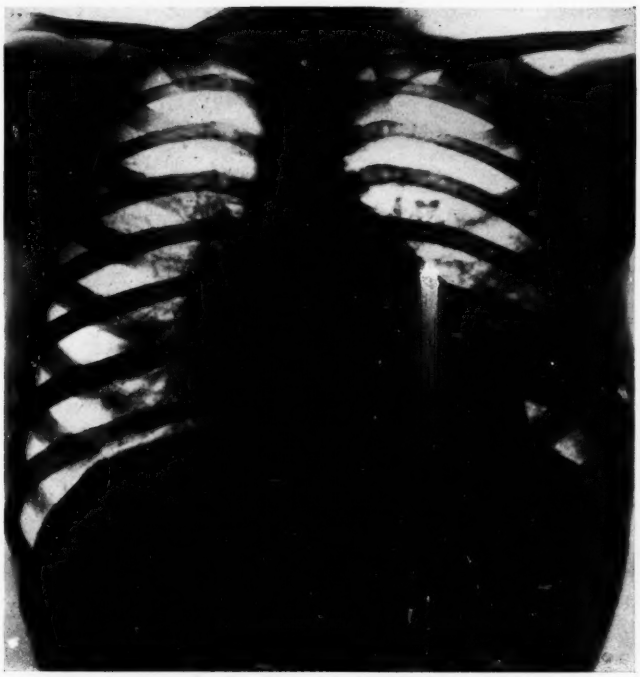

FIG. 4*b*

616.37-007.415-08

THE TREATMENT OF SPONTANEOUS HYPOGLYCAEMIA DUE TO HYPERPLASIA OF THE ISLETS OF LANGERHANS[1]

By GEORGE GRAHAM and WILFRID G. OAKLEY

(From St. Bartholomew's Hospital, London, and
King's College Hospital, London)

With Plate 2

Introduction

Spontaneous hypoglycaemia is an uncommon condition which is due to various causes:

I. *Functional disturbances of the carbohydrate metabolism.* (*a*) For some reason the blood-sugar after meals rises, from a normal figure of 70 to 110 mg. per 100 c.c., considerably higher than the usual figure of 130 to 150 mg., and may exceed 250 mg. per c.c. After a period of three to five hours the blood-sugar falls to a lower level than normal, and may be as low as 50 mg. per 100 c.c. During this hypoglycaemic phase the patient may experience hunger, weakness, ataxia, irritability, and sweating. According to Conn (1940) such attacks seldom last for more than 15 minutes, and pass off with rest without the giving of sugar; they are rare after midnight. Coma is very uncommon, and fits never occur. There is no tendency for this condition to progress, and there may be long remissions in which the patient is free from all symptoms. The cause is not known, but it is most often seen in patients with an unstable autonomic nervous system (Wilder, 1940) and, as in the next condition to be described, may be associated with rapid emptying of the stomach. This form of functional hypoglycaemia may be prevented by the addition of buffer carbohydrate feeds between the usual meals. If this fails, relief may be obtained by the use of a high protein (100 to 130 gm.) and low carbohydrate (100 gm.) diet.

(*b*) A syndrome occurring after gastro-enterostomy or partial gastrectomy. This condition has been studied by Kalk and Meyer (1932), Beckermann (1933), Lapp and Dibold (1933), Korányi (1936), Wöhrle (1936), Evenson (1942), Adlersberg and Hammerschlag (1947), Gilbert and Dunlop (1947), and Barnes (1947). The most detailed account is given by Evenson. He found that symptoms associated with hypoglycaemia occurred in three out of 50 normal persons, in four out of 50 patients who suffered from gastric or duodenal ulcers, in 11 out of 38 patients who had a gastro-enterostomy, and in 12 out of 98 patients on whom a partial gastrectomy had been performed. The patients who complained of symptoms had the type of sugar-tolerance curve already described. Glycosuria was usually present whenever the blood-sugar was more than 180

[1] Received April 23, 1949.

to 200 mg. per 100 c.c., and it was this circumstance which first attracted attention, since it was necessary to exclude the diagnosis of diabetes mellitus. The discovery of the hypoglycaemia then suggested an explanation of the so-called 'dumping' syndrome, in which the symptoms are similar to those of functional hypoglycaemia, and may be so severe as to incapacitate the patient. If these occur from one and a half to three hours after the meal, it is probable that they are due to hypoglycaemia, and the diagnosis can be clinched by estimating the blood-sugar at the time when the symptoms are most severe. Some patients complain of these symptoms much sooner after meals, and since the blood-sugar may either be high or within normal limits at this time, another cause must be assumed. It is generally believed that sugar is absorbed into the blood more quickly than usual owing to a rapid emptying of the stomach contents into the duodenum, and that insulin is not secreted quickly enough to prevent the excessive increase of blood-sugar. Hypoglycaemia occurs because the patient either secretes too much insulin or is unusually sensitive to it.

Treatment is not easy, but Gilbert and Dunlop (1947) had some success with high fat diets, or the administration of one ounce of olive oil before meals. They also recommended the trial of ephedrine sulphate, gr. ½ half an hour before the three main meals. Hastings-James (1949) also had good results with a high fat diet.

II. *Excessive production of insulin due to*: (*a*) an adenoma of the islets of Langerhans; (*b*) a malignant tumour of the islets of Langerhans; (*c*) hyperplasia of the beta cells of the islets of Langerhans. These three conditions are very rare in comparison with the other causes of hypoglycaemia. The symptoms and diagnosis are described later on in connexion with the patient who forms the subject of this paper. Once the diagnosis has been established, the best treatment is the removal of the tumour; if it is innocent the patient recovers completely, but if it is malignant and secondaries have occurred, the hypoglycaemia persists in spite of the removal of the primary tumour. If the hypoglycaemia is due to diffuse hyperplasia of the islets, it may persist in spite of the removal of practically the whole of the pancreas. In this condition the following methods of treatment may be tried:

1. Treatment with Young's crude extract of the anterior pituitary gland, which causes diabetes in dogs (Young, 1937).
2. Injection of alloxan, which has a selective necrotic action on the islet cells in animals (Dunn, Sheehan, and McLetchie, 1943).
3. Treatment with deep X-rays.

Case Report

The three methods just mentioned have been used in the treatment of a patient who had a diffuse hyperplasia of the islet cells. The patient, a German-Jewish refugee aged 53, was first seen by us in February 1941. She was then grossly overweight, as a result of having to take sugar repeatedly to prevent attacks of hypoglycaemia; these recurred at frequent intervals throughout the

24 hours. There was nothing significant in her past history. Physical examination showed the presence of severe bilateral keratoconus, which greatly impaired her vision. The thyroid was firm, and uniformly enlarged to a slight extent, but there was no evidence of its toxicity. The heart and lungs appeared normal on clinical and radiological examination, and her blood-pressure was 150/90 mm. Hg. Apart from excess of subcutaneous fat, and the scar of a previous operation, there were no abnormal signs in the abdomen, and a cholecystogram did not show any evidence of disease of the gall-bladder. The blood-count was normal, the urine did not contain any sugar, albumin, or acetone bodies, and the results of renal function tests were within normal limits.

In 1934, while in Hamburg, she had her first attack of coma, the cause of which was not diagnosed. In 1937 she developed fits, which were at first attributed to epilepsy, but in the following year were shown to be due to hypoglycaemia. She came to England in 1939, and was then taking glucose with all meals and twice during the night, attacks of hypoglycaemia being most common between 6 a.m. and 8 a.m. In November 1939 she was in the Edinburgh Royal Infirmary under the care of Professor Dunlop, who confirmed the diagnosis. The pancreas was explored by Sir John Fraser and the central portions of the gland removed, since a thickening suggesting a tumour was felt; the section, however, showed normal pancreatic tissue only, and the patient relapsed eight days after operation.

In February 1941 she came under our care, and exhibited typical hypoglycaemic attacks in which she first became emotional and difficult, then excitable and violent, then incoherent, and finally comatose; sweating, when present, was a late sign. During two such attacks the blood-sugar was found to be 43 and 45 mg. per 100 c.c. respectively; the usual fasting level was between 50 and 60 mg. per 100 c.c. Drinks sweetened with glucose, if given early enough, always aborted the attacks, but if saccharine was substituted without the patient's knowledge, she was not relieved. The three criteria of A. O. Whipple (Wilder, 1940) for the diagnosis of spontaneous hypoglycaemia were therefore fulfilled, viz.: 1. The attacks occurred while fasting. 2. The attacks were relieved by glucose when given without the patient's knowledge. 3. A blood-sugar of less than 50 mg. per 100 c.c. was present during the attacks. Wilder (1940) further suggested that the autonomic system should have been stable before the onset of the symptoms, and our patient was apparently quite normal in this respect prior to 1934.

Blood-sugar curves were estimated before and after the various forms of treatment which the patient received during the following four years (Figs. 2, 3, 6, 7). The patient was very anxious to avoid a second operation, since a fistula developed after the first and had taken a long time to heal. An attempt was therefore made to destroy the islet cells by Young's crude anterior pituitary extract.

Treatment with anterior pituitary extract. This was begun in March 1941, and is summarized in Fig. 1. Five c.c. were given intramuscularly on the first day, and 10 c.c. daily for the next four days, after which the dose was increased

to 15 c.c. a day for four days, and then to 20 c.c. for three days. After a few injections the patient showed slight but definite improvement, since she was able to do without the 3 a.m. feed, but the blood-sugar curve after 165 c.c. of extract (41·25 gm. fresh ox pituitary) had been given showed no change in glucose-tolerance, and a week later the 3 a.m. feed again became necessary. After an interval of nine days, due to a temporary failure in supply of the

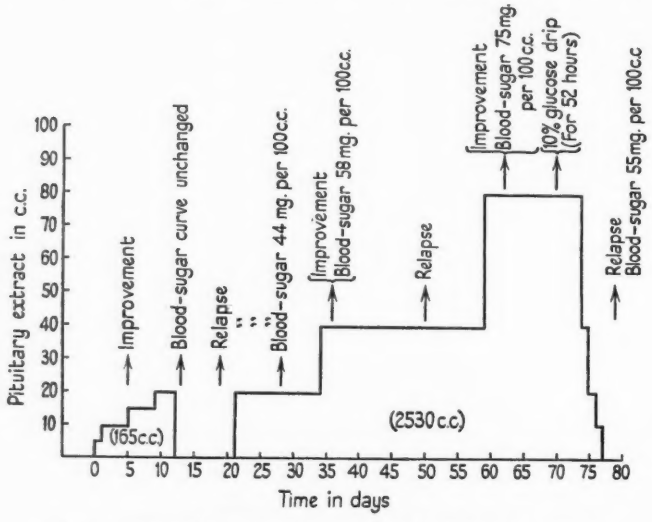

FIG. 1. Shows the amount in c.c. of crude pituitary extract injected in the course of 77 days.

extract, treatment was continued with 20 c.c. daily for 13 days, but this time there was no improvement, and after a week the fasting blood-sugar was 44 mg. per 100 c.c. It was therefore decided to increase the dose to 40 c.c. daily, and this was given for the next 25 days, making a total dosage of 1,000 c.c. (250 gm. fresh ox pituitary) for this period, and 1,425 c.c. in all. After two days of the increased dose of 40 c.c., clinical improvement was again noted and the 3 a.m. feed was discontinued. After 10 days attacks began to recur, and two weeks later the dose was raised to 80 c.c. daily for 15 days, with almost immediate cessation of attacks. The fasting blood-sugar on two occasions was 75 mg. and 79 mg. per 100 c.c. During this last course of injections the patient was given a 10 per cent. glucose drip for 52 hours in order to throw a greater strain on the islet tissue, but this had to be stopped because of phlebitis. The patient had no further attacks for three days after cessation of treatment, but began to relapse in the following week. In all, 2,695 c.c. of extract (673·75 gm. fresh ox pituitary) were given, without any change being noted in the blood-sugar curve (Fig. 2). It was considered that, apart from the difficulty in preparing such large amounts of pituitary extract, it was not practicable to inject more than 40 c.c. twice a day intramuscularly, because of the increasing severity of local reactions.

Treatment by operation. We therefore decided to have the pancreas explored again, in the hopes of finding a tumour, and if not, of removing the whole of the gland. The operation, which was performed by E. W. Riches, was very difficult owing to the numerous dense adhesions. A good view was obtained of the pancreas, which consisted of two portions of almost equal size, since the central portion of the body had been removed at the previous operation. A tumour

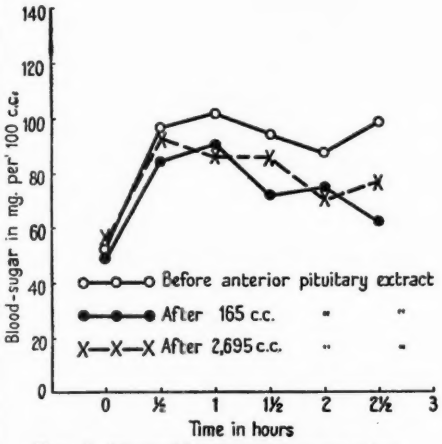

FIG. 2. Shows blood-sugar curves after 100 gm. glucose.

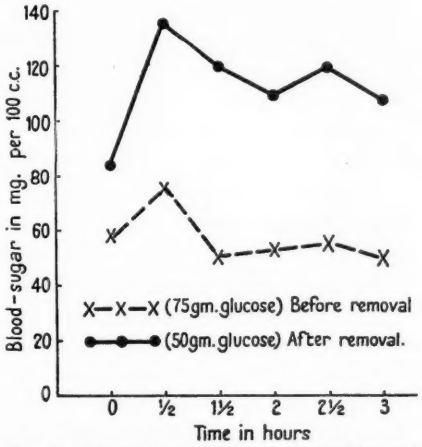

FIG. 3. Shows blood-sugar curves before and after removal of the head of the pancreas.

could not be found, and the tail of the pancreas was excised; the spleen was removed at the same time, as it simplified the procedure.

The patient had no attacks for a week after the operation, but then relapsed, with a blood-sugar of 48 mg. per 100 c.c. Three months later the patient's abdomen was again opened, and, in spite of great technical difficulties, almost all the remaining pancreatic tissue, consisting chiefly of the head of the gland, was successfully excised. Immediately after operation the blood-sugar rose to 250 mg. per 100 c.c., and the fasting level seven weeks later was 100 mg. per 100 c.c.; clinical recovery was complete, and the patient remained free of symptoms for two years, during which, as a result of reducing the carbohydrate intake, she lost 28 lb. in weight. Sections of the head of the pancreas showed simple hyperplasia of the islets of Langerhans, without any of the characters of malignant disease (Plate 2, Figs. 4 and 5). The islets appear to be several times larger than normal, their cells and nuclei being uniform in size and shape. In the sections of the head, the islets are prominent in all lobules and abnormally large; there is a decided increase in the number of islets per unit area, this increase being almost as striking as that in size.

In 1943 (almost exactly two years after the removal of the pancreas) slight symptoms of hypoglycaemia began to reappear, but there was no actual loss of consciousness. The symptoms persisted and became gradually more severe during the next 14 months. Fasting blood-sugars of 46 mg. and 49 mg. per

100 c.c. were again recorded, and the patient needed glucose between meals and during the night to prevent attacks of coma.

Treatment with alloxan. In 1943 Dunn and his fellow workers published their results on the experimental production of diabetes in animals with alloxan. In October 1944 it was decided to try to destroy the islet cells with alloxan, and the patient was given 500 c.c. of a 5 per cent. solution of alloxan (25 gm.) intravenously. The infusion was given into an ankle vein, but after the first hour the patient had a rigor and complained of severe pain in the leg; this was followed by swelling of the limb and intense tenderness along the course of the vein, so that after three hours the alloxan was stopped, and normal saline was used in order to keep the drip running. Next day the fasting blood-sugar was 49 mg. per 100 c.c., and a further 500 c.c. of a 5 per cent. solution of alloxan (25 gm.) were given. This again produced intense pain, swelling, redness, and vesiculation of the skin of the leg, and it was necessary to keep the patient under morphia during the latter part of the infusion. On the third day the fasting blood-sugar was 130 mg. per 100 c.c., and the patient was given 1,120 c.c. of a 2·5 per cent. solution of alloxan (28 gm.), since the local reaction to the 5 per cent. solution had been so severe. At the end of this infusion a second rigor occurred with vomiting, but the patient's general condition remained good, and less carbohydrate was required to prevent attacks. The urine after this infusion was noticed to be pink, but contained no sugar, acetone bodies, or albumin. Altogether the patient received 78 gm. of alloxan, or 1 gm. per kg. of body-weight. During the following week the fasting blood-sugar varied between 61 and 72 mg. per 100 c.c., and glucose had to be given at 10 p.m., 1 a.m., and 4 a.m. only, instead of every two hours. By the seventeenth day, however, the fasting blood-sugar had fallen to 45 mg. per 100 c.c., and a complete relapse occurred.

A second attempt was made three weeks later, when 6,450 c.c. of a 1·5 per cent. solution of alloxan (90 gm.) were given intravenously over a period of three days. During the third day the patient suddenly developed severe tetany, with muscular stiffness affecting the face, abdomen, and limbs, Chvostek's sign being strongly positive. Fifteen c.c. of a 10 per cent. solution of calcium gluconate were given intravenously without much effect, and one hour later 60 units of parathormone were injected, which relieved her considerably. A further 15 c.c. of calcium gluconate were given an hour later, and by the next morning the tetany had disappeared. The urine again became deep pink after about 50 gm. of alloxan had been given, but was normal in colour before the end of the infusion. The fasting blood-sugar for the next few days was between 70 and 80 mg. per 100 c.c., and glucose feeds were again reduced. A severe phlebitis with abscess formation and swinging fever ensued, during which the patient was entirely free from symptoms of hypoglycaemia for five weeks, although she did not have any extra feeds. She then had a severe attack of hypoglycaemia at 8 a.m., i.e. after a 12-hour fast, the blood-sugar being 36 mg. per 100 c.c.

Treatment by X-rays. As a last resort it was decided in March 1945 to try

to destroy the islet cells by deep X-rays. The patient was treated at St. Bartholomew's Hospital with the million-volt apparatus, and received the following dosage from March 15 to April 24: anterior and posterior abdominal fields (field size 11 ×11 cm., focus–skin distance 70 cm.), skin dose to each field 3,660 r, tumour dose 2,500 r in 40 days. A week later the patient was able to do without feeds during the night, and the blood-sugar curve showed marked

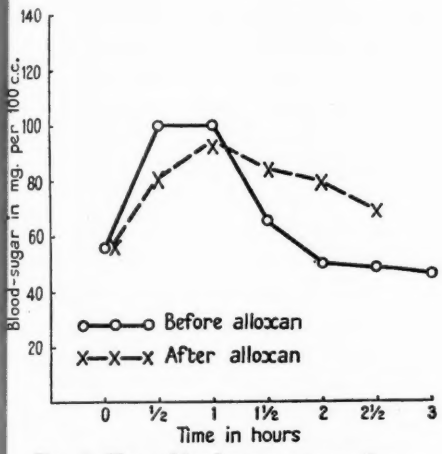

FIG. 6. Shows blood-sugar curves after 50 gm. glucose.

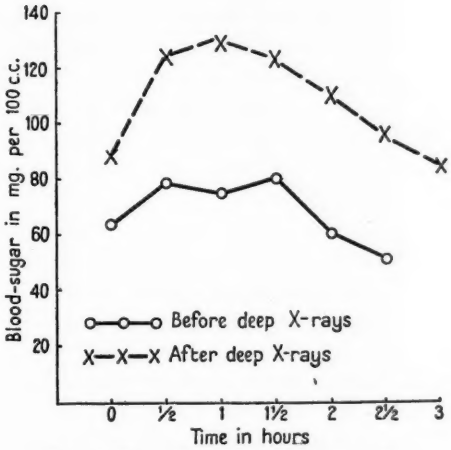

FIG. 7. Shows blood-sugar curves after 50 gm. glucose.

improvement (Fig. 7). The improvement lasted for about two months, when she began to relapse and could not be without extra carbohydrate for longer than 11 p.m. to 6 a.m. The results of the first course of X-rays were, however, so encouraging that the patient begged us to let her have a second. A further treatment with the million-volt machine was accordingly given, six months after the first, from October 1 to November 5, 1945: anterior and posterior right and left oblique abdominal fields (field size 11 ×11 cm., focus–skin distance 70 cm.), skin dose to each of the four fields 1,700 r, tumour dose 2,500 r in 36 days.

Once more it was possible to reduce the night feeds, and a state was reached in which the patient was able to avoid hypoglycaemia fairly easily, by spacing her meals at three-hourly intervals during the day, and setting her alarum clock for 6 a.m., when 20 gm. of glucose was taken. In a letter received in May 1948 from Jerusalem the patient stated that she was well, but that she still required a dose of glucose in the early morning.

Discussion

The diagnosis did not present any difficulty, and the chief interest lies firstly in the pathological lesion, and secondly in the treatment.

Pathological lesion. The commonest cause of true hyper-insulinism is an adenoma of the islet tissue, but carcinoma is not very rare. The occurrence of

spontaneous hypoglycaemia due to hyperplasia is more doubtful. This diagnosis has been made by Phillips (1931), Malamud and Grosh (1938), and Agustsson, Tudor, and Chisholm (1947). The presence of unusually large islets is stressed, but there is such great variation in the size of normal islets (K. C. Richardson, personal communication) that it is impossible to be dogmatic on this point. An increase both in the number and in the size of the islets is more suggestive; but to be conclusive, quantitative estimations of number and size are essential, and this has so far not been reported. In our patient, firstly the failure to find a tumour in spite of careful search at three operations, secondly, the remission of all symptoms for two years after the almost complete removal of the pancreas (followed by a very gradual relapse), and thirdly, the good response to deep X-rays accurately applied to the remains of the head of the pancreas, offer, we consider, convincing evidence for the diagnosis of hyperplasia of the islet cells.

Treatment. The response of our patient to pituitary extract has a slight resemblance to that obtained by Young (1937) in his experiment on dogs. He showed that in order to make dogs diabetic it was essential to produce hyperglycaemia, and that as soon as hyperglycaemia began to decrease, the dose of pituitary extract had to be doubled in order to maintain it. Diabetes was usually produced after the dose had been doubled three or four times. Our patient received a total of 2,695 c.c. of pituitary extract, representing 673·75 gm. fresh gland, and although there was a definite rise in the blood-sugar and some clinical improvement, hyperglycaemia was never observed. The smooth course of the treatment may have been affected by a break of nine days in the treatment, and by the fact that the maximum dose tolerated by the patient was 80 c.c. daily. The reason why the pituitary extract did not produce diabetes may have been the failure to produce hyperglycaemia. Conn and Louis (1945) reported the results of the injection of anterior pituitary extract in two patients suffering from spontaneous hypoglycaemia, in both of whom they observed that the daily injection of an amount of extract equivalent to 10 gm. of gland resulted in a sharp fall in the fasting blood-sugar level; an equally abrupt rise occurred when the extract was discontinued. From this they concluded that anterior pituitary extract contains an insulogenic or insulotropic principle which acts by directly stimulating the insulin-producing cells of the islets of Langerhans. They suggested that this principle exhausts the islets, and is responsible for the initiation of hyperglycaemia in normal dogs. On this hypothesis, if the stimulus could be made too great for the capacity of the islet tissue to respond, eventual degeneration of all islet tissue, including tumour tissue, should take place. The findings in our case lend no support to this hypothesis, but if it is correct, the sole reason for failure in all three cases was inadequate dosage of anterior pituitary extract.

Our failure to relieve the hypoglycaemia with alloxan was disappointing. There was no indication of an initial aggravation of hypoglycaemia, such as occurred in experimental animals. This hypoglycaemia is thought to be due to liberation of large amounts of insulin from the damaged islet cells. In its

absence, any destruction of the cells seemed most unlikely, and such proved to be the case. The reason for the failure of alloxan to produce islet necrosis may have been inadequate dosage, although the dose of one gramme per kilogram exceeded that required to produce permanent diabetes in dogs. Another possible explanation is that the concentration of alloxan in the blood and tissue was too low; against this is the view, based on animal experiments, that the islet tissue takes up and concentrates the alloxan, so that the amount in the blood at any one time is less important than the total dosage given. Walpole and Innes (1946) showed that if the pancreatic duct is tied in the rabbit, and the acinar tissue allowed to atrophy, the destructive action of alloxan on the islet tissue is greatly reduced. In our patient the acinar tissue had been completely removed by operation, and it is therefore possible that the action of alloxan was inhibited for this reason.

The importance of species variation cannot be ignored as a possible explanation of our failure with both anterior pituitary extract and alloxan. Brunschwig (1944) favoured this explanation in the case of alloxan, but Conn and Hinerman (1948) concluded that its destructive effect on the human pancreas approximates to that observed in other species. Brunschwig, Allan, Owens, and Thornton (1944) gave alloxan to two patients with spontaneous hypoglycaemia. In the first, a primary carcinoma of the islets had been removed two years previously, and the symptoms of hypoglycaemia were due to secondary deposits. Alloxan was given at irregular intervals during 51 days, making a total of 2·72 gm. per kg. of body-weight. The alloxan injections were followed by improvement and relapses, and eventually the patient demanded a further operation. Metastases were found, and the patient died suddenly the next day. The section did not show any changes in the islet cells. The second patient was very ill with secondary carcinomatosis, but had no symptoms of hypoglycaemia. An injection of 60 mg. of alloxan per kg. of body-weight was given, and the patient died six hours later. The sections showed doubtful evidence of injury to some of the islet cells, but many were unaffected. The duration of alloxan action, six hours, was perhaps too short to allow of more extensive changes. Conn and Hinerman (1948) treated a patient, suffering from an adenoma of the islet tissue, with 50 mg. of alloxan per kg. of body-weight for two days, and with 100 mg. per kg. for seven days. The total dose was 60 gm., or 0·8 gm. per kg. The fasting blood-sugar remained low, but the carbohydrate tolerance was slightly diminished. Fifteen days later the adenoma was removed. Twenty hours after the operation glycosuria appeared, and the blood-sugar was 200 mg. per 100 c.c. The diabetes became worse, and as much as 60 units of insulin were needed to lower the blood-sugar to within normal limits; a low carbohydrate diet was given at this time. The diabetes improved while the low carbohydrate was taken, and insulin was soon unnecessary. At histological examination the cells of the adenoma were normal in appearance, but the islet cells of the rest of the pancreas showed marked changes. One hundred and twenty-eight islets were counted, of which 33 per cent. showed very little alteration, 21 per cent. varying degrees of change, 26 per cent. severe damage,

15 per cent. complete destruction, and 5 per cent. hyperplasia; of the cells, 82 per cent. were alpha and delta, and 18 per cent. beta cells. A normal islet contains approximately the same number of beta cells as of alpha and delta cells together.

These findings suggest two possible explanations for the failure of alloxan in the present case: either that the hypoglycaemia was due to an islet adenoma which escaped removal at operation, or that hyperplastic islet tissue resembles adenoma in its resistance to the destructive action of alloxan. The arguments in favour of the diagnosis of diffuse hyperplasia are, in our opinion, conclusive. But this does not prove that the hyperplastic cells are resistant to alloxan. The great mass of the pancreas had been removed before it was given, and Walpole and Innes showed that this reduces the action of alloxan.

Summary

1. The case is described of a woman of 53, who had spontaneous hypoglycaemia due to a diffuse hyperplasia of the islets of Langerhans.

2. An attempt to destroy the islet cells with Young's crude anterior pituitary extract (673·75 gm.) produced a transient improvement, but was a failure.

3. Removal of nearly the whole of the pancreas in two stages caused a remission of all symptoms for two years.

4. Alloxan, 168 gm. (1 gm. per kg. of body-weight in each experiment) failed to destroy the islet cells.

5. Treatment with X-rays caused a definite improvement in the condition, which has been maintained for two years and eight months.

We wish to express our thanks to Professor F. G. Young, not only for providing us with the anterior pituitary extract, but also for his valuable advice; to Mr. E. W. Riches, who carried out the very difficult operations; to Professor W. G. Barnard, the late Dr. E. ff. Creed, Dr. J. G. Greenfield, Professor G. F. Hadfield, and Dr. K. C. Richardson, who examined and reported on the sections; and to Sister O'Callaghan of St. Andrew's Hospital, for her skilful and devoted care of a most difficult case.

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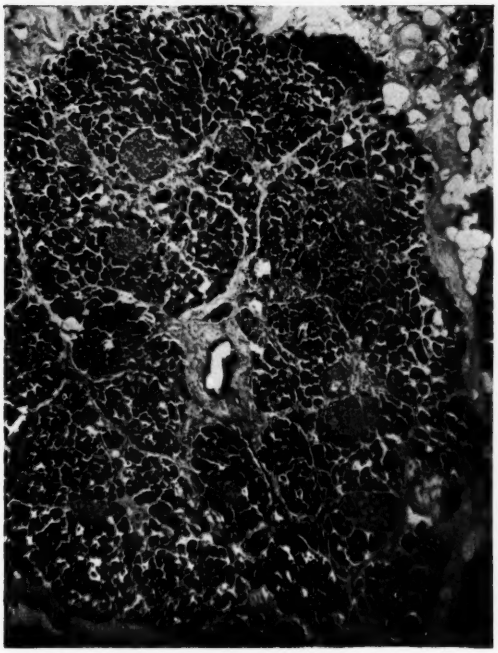

FIG. 4. Shows the pancreas with a number of islets ×48 approximately

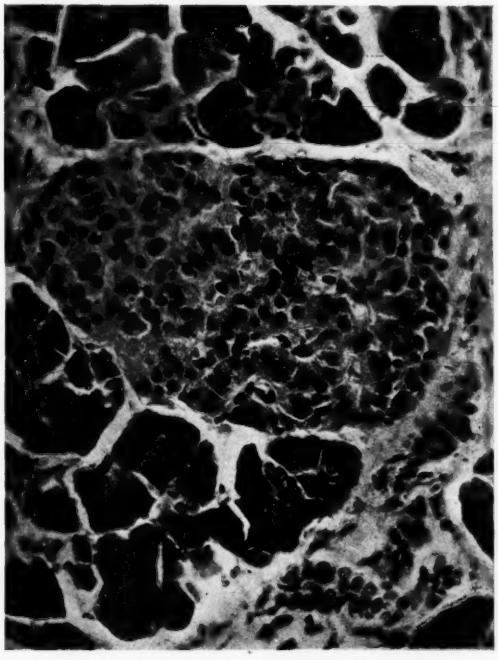

FIG. 5. Shows an islet ×350 approximately

616.61

A CLINICAL AND PATHOLOGICAL STUDY OF RENAL DISEASE

PART II. DISEASES OTHER THAN NEPHRITIS[1]

By ROBERT PLATT and J. DAVSON

(From the Departments of Medicine and Pathology, Manchester University)

With Plates 3 to 6

The original purpose of this investigation was to test the validity of Ellis's (1942) classification of nephritis by studying the pathological material and case records from a large number of fatal cases of renal disease. The whole series comprises 188 cases, collected over an 11-year period, of which 48 were classed as Type 1 or Type 2 nephritis and have already been described in Part I of the investigation (Davson and Platt, 1949) and 14 were diagnosed as periarteritis nodosa and described separately (Davson, Ball, and Platt, 1948). The present paper deals with the remaining 126 cases.

The reader is referred to Part I of the investigation for a full account of the method of study. In brief the plan was for the clinician to examine the clinical records of the patients, many of whom he had himself seen during life, while the pathologist independently studied the histological sections. Each came to his own diagnostic conclusions which were later compared and discussed. Table 1 shows the distribution of the 188 cases according to the final diagnosis, and also gives the number of patients in each group who died of renal failure, as shown by gross elevation of the blood-urea during life. It will be seen that apart from Type 1 and Type 2 nephritis the most important conditions leading to death from renal failure are pyelonephritis and malignant hypertension. Periarteritis nodosa, hydronephrosis, and diabetic glomerulosclerosis are also numerically important amongst the causes of death from renal disease. In clinical experience benign hypertension is, of course, far more common than the malignant form, but it rarely leads to a gross disturbance of renal structure or function, and therefore does not figure largely in a survey of this kind based on a series of cases selected by the finding of macroscopic renal pathology at post-mortem examination. It is also probable that the victims of benign hypertension, being frequently persons of advanced years, are not found so often amongst the post-mortem records of a teaching hospital. Unfortunately, cases showing the renal lesions of bacterial endocarditis were not included in the present series, which also contains no case of polycystic disease or of hypercalcaemia. Renal failure secondary to prostatic enlargement is also not

[1] Received June 21, 1949.

included, as the material is derived from the medical wards. These are, we think, the only important causes of renal disease not included.

We propose now to describe briefly the clinical and pathological features of some of these renal disorders, the object being not to present a complete account, but rather to record the lessons we have learnt from the study of this material.

TABLE I

Clinico-pathological Diagnosis in 188 Cases of Renal Disease

	Death from renal failure	*Total*
Type 1 nephritis	21	23
Type 2 nephritis	17	25
Pyelonephritis	18	26
Malignant hypertension	21	24
Benign hypertension	5	16
Periarteritis nodosa	11	15*
Hydronephrosis	8	11
Diabetic glomerulosclerosis	6	9
Hypoplastic kidney	5	9
Dehydration or anoxia	6	10
Pregnancy kidney	2	2
Amyloid disease	3	3
Myelomatosis	2	3
Disseminated lupus erythematosus	1	2
Pheochromocytoma	1	1
Renal tuberculosis	1	1
Scleroderma	1	1
Miscellaneous	7	7
	136	188

* Includes Case 8.

Pyelonephritis (26 cases)

Clinical features. Although the *pyelonephritische Schrumpfniere* was described by German authors many years ago, little was known of the clinical course of chronic pyelonephritis until Longcope and Winkenwerder (1933) discussed its significance, and there was no general recognition of its importance as a cause of hypertension and renal failure until the monograph of Weiss and Parker (1939). Clinically pyelonephritis may appear in the following ways:

1. As an acute febrile illness often with rigor, pain in the loin, and dysuria, the so-called acute pyelitis.
2. As an illness characterized by chronic backache, frequency, and dysuria, all of which may be very slight, and punctuated by more acute attacks of cystitis or pyelitis. Often the patient states that she has these symptoms whenever she 'gets a chill'. On inquiry it seems fairly clear that the chill is not associated with any communicable infectious disease and is in fact the result, and not the cause, of an exacerbation of the urinary infection.
3. Acute or chronic urinary infection may be a complication of obvious or obscure urological disease such as hydronephrosis, enlarged prostate, calculus, and hypoplastic kidney; or of disease of the nervous system.

4. The patient may be seen on account of symptoms of chronic renal failure, hypertension, or both, the cause of which is not immediately apparent. These cases have often been diagnosed in the past as chronic interstitial nephritis or malignant hypertension.

As all but three of the cases in the present series were self-selected by their fatal outcome, they belong to the fourth group. In the three non-fatal cases

TABLE II

Chronic Pyelonephritis

Age (years)	*Cases*	*Hyper-tension*	*Renal failure*	*Both*	*Calculus present*
20 to 29	8	3	6	1	1
30 to 39	9	7	5	4	1
40 to 49	3	2	2	1	1
50 to 59	1	0	1	0	0
60 to 69	4	2	3	2	0
70 and over	1	0	1	0	1
	26	14	18	8	4

kidneys were removed for presumed unilateral disease and hypertension, but without success. In four cases calculus was also present, but whether this was the cause or the result of the pyelonephritis we do not know. We have no information as to how often acute or chronic urinary infections are followed by renal failure or hypertension.

We would particularly stress the fact that symptoms and signs of urinary infection may be absent when the case is seen in an advanced stage, and cultures of the urine may be negative. Albuminuria is usually constant in the uraemic cases, but may be absent in those presenting as hypertension. A correct clinical diagnosis can usually be made on the history of chronic or recurrent urinary infection together with the absence of any other cause of hypertension or renal failure. Fourteen of the 26 cases were seen by one of us (R. P.) during life and the correct diagnosis was made or suspected in 12. Patients may show evidence of renal failure (weakness, vomiting, dry skin, anaemia, nocturia, albuminuria, high blood-urea) or hypertension (headache, retinopathy, cardiac failure, cerebral vascular lesions). Both frequently coexist, and a diagnosis of malignant hypertension is therefore often wrongly made. Case 1 represents the uraemic, Case 2 the hypertensive, and Case 3 the mixed type (these are described in the Appendix).

Of our 26 fatal cases of chronic pyelonephritis 16 (62 per cent.) were female. The age incidence and the frequency of hypertension and renal failure are shown in Table II. It will be seen that almost two-thirds were under 40 years, an age at which malignant hypertension is unusual (Platt, 1948).

In cases where the renal failure of pyelonephritis is unaccompanied by severe hypertension, the uraemic symptoms may be extraordinarily chronic, and the patient may be admitted to hospital with the diagnosis of anaemia (Case 1). In younger patients the changes in mineral metabolism due to prolonged renal failure may lead to the syndrome of renal rickets. In such cases (to be

described later) hypoplastic kidney is often an underlying cause of the urinary infection.

In addition to the 26 cases in which chronic pyelonephritis was apparently the main disease, many of the patients described under hydronephrosis and hypoplastic kidney had pyelonephritis in addition. As our material is derived almost exclusively from the medical wards, cases of pyelonephritis complicating prostatic disease are not included.

Pathological aspects of chronic pyelonephritis. It is not difficult to recognize that a contracted and granular kidney is the result of chronic pyelonephritis when evidence of urinary obstruction such as an impacted calculus, hydronephrosis, or dilated ureter is also present. When such evidence is lacking, and the renal changes are bilateral, the distinction between chronic atrophic pyelonephritis and other types of granular kidney, such as slowly progressive Type 1 nephritis, or ischaemic atrophy secondary to hypertension or atheroma, is not always easy at autopsy. Weiss and Parker (1939) have pointed out that variation in size between the two kidneys may be helpful in the diagnosis of chronic pyelonephritis. In our group of 26 cases the weights of the kidneys were recorded in 14 instances. In seven one kidney weighed at least twice as much as the other, whereas in eight cases of slowly progressive Type 1 nephritis in which weights were known no such disproportion was found. Our results, therefore, tend to confirm the view of Weiss and Parker that marked inequality in renal size may characterize chronic atrophic pyelonephritis. A further point is that the total loss of nephrons appears to be greater in chronic pyelonephritis than in slowly progressive Type 1 nephritis. The average of the combined weights of the kidneys in 14 cases of pyelonephritis with known renal weights was 110 gm. compared with 152 gm. in the eight cases of slowly progressive Type 1 nephritis. Gibson (1928) and Fahr (1938) have mentioned the irregular involvement of the kidney substance by pyelonephritis, areas of unaffected cortex separating atrophic areas; this observation was made macroscopically in many of our cases. Gibson (1928), Kimmelstiel and Wilson (1936*a*), Weiss and Parker (1939), Bell (1942), Likely, Lisa, and Solomon (1942) have all drawn attention to the coarse surface scarring that is seen in chronic pyelonephritis. In 20 cases the kidneys were contracted and granular (Plate 3, Fig. 1), and in 10 of these coarse scarring (Plate 3, Fig. 2) was noted in the autopsy records. Coarse scarring was not reported in any of our cases of slowly progressive Type 1 nephritis or of hypertensive nephrosclerosis. The degree of loss of architecture of the kidney as shown by the cut surface varied, but severe loss of pattern was recorded in 10 cases, which included the most severely contracted kidneys.

Histology. The histological appearances in chronic atrophic pyelonephritis vary somewhat according to the stage of the disease and with the presence or absence of active inflammation. Areas of fibrosis and round cell infiltration involve cortex and medulla, and groups of completely fibrotic glomeruli may be seen in the cortex. Periglomerular fibrosis may be frequent, and fibrous adhesions of the tufts to the capsule occur, but epithelial crescent formation is rarely seen. Evidence of activity is shown by intense round cell and poly-

morphonuclear infiltration in the medulla, becoming progressively more intense as the pelvis is approached; this was noted in 12 cases. A further sign of active inflammation is the presence of polymorphonuclear cells in the tubules, which occurred in six cases. Evidence of past activity, in addition to fibrotic glomeruli and interstitial fibrosis, is provided by the presence of areas of tubules containing so-called 'colloid' casts, closely resembling thyroid tissue (Plate 3, Fig. 3). Such areas are regarded as pathognomic of the healed stage of pyelonephritis by Weiss and Parker (1939). In our group of 26 cases they were present in 14, and appeared to be characteristic, as we have not found them in other forms of nephropathy. Confirmation of the diagnosis of chronic pyelonephritis is found in the pelvis, where round cell and polymorphonuclear infiltration and varying degrees of fibrosis of the pelvic wall are seen. Such infiltration was present in 19 cases of this group; in the rest no pelvic tissue was present in the sections available.

Relation to hypertension. Weiss and Parker pointed out the frequency with which chronic pyelonephritis is associated with hypertension, and numerous authors have subsequently confirmed this statement. In 25 of our patients with pyelonephritis the blood-pressure was recorded, and hypertension was present in 14. These figures, though small, tend to confirm the association of chronic pyelonephritis and hypertension. Histological evidence of hypertension was present in all 14, in the form of arteriosclerosis, and in four of these fibrinoid necrosis of arterioles and glomeruli, together with endarteritis fibrosa, indicated that the condition of malignant nephrosclerosis was present. Owing to the essentially patchy involvement of the renal parenchyma by the pyelonephritic process, examination of a single block of kidney may show only changes that could be regarded as secondary to hypertension, whereas other areas may show the characteristic changes of chronic pyelonephritis. This emphasizes the necessity for the examination of numerous blocks of tissue in a case of contracted kidneys, and also shows that renal biopsy in cases of hypertension may have limited value in excluding pyelonephritis, since the amount of tissue removed is small.

Differential diagnosis. As Ellis (1942) has pointed out, the chief condition with which chronic pyelonephritis has been confused is slowly progressive Type 1 nephritis. The naked-eye features which suggest pyelonephritis rather than Type 1 nephritis are the difference in size of the kidneys, coarse scarring of the surface rather than fine, and the presence of unaffected areas of cortex lying adjacent to contracted areas. Histologically, features indicative of pyelonephritis rather than chronic Type 1 nephritis are inflammatory infiltration of the wall of the pelvis, foci of fibrosis in the pyramids, thyroid-like areas of tubules, round cell infiltration in the medulla increasing in intensity near the pelvis, and polymorphonuclear cells in the tubules. From rapidly progressive Type 1 nephritis the differential diagnosis is less difficult; in this condition there is neither gross contraction of the kidneys nor coarse scarring, no large areas of unaffected nephrons are seen, and the pelvis is unaffected. However, one case of rapidly progressive Type 1 nephritis was encountered, which has

already been referred to in the preceding communication, in which active pyelonephritis was present, apparently as a complication, and in this case the double diagnosis was made.

The diagnosis from malignant hypertension may cause difficulty in cases where the glomerular and vascular lesions of hypertension have developed terminally in a case of chronic pyelonephritis. If, however, the naked-eye and histological characteristics of chronic pyelonephritis already enumerated are sought for and found, it is not difficult to recognize the essentially superimposed nature of the lesions of malignant nephrosclerosis. The presence of polymorphonuclear cells in the large eosinophilic casts, which are often seen in dilated cortical tubules in malignant hypertension, may cause difficulty. Two patients should be specially mentioned, both young subjects with the clinical syndrome of malignant hypertension; in each case the kidneys showed the typical features of malignant nephrosclerosis together with unequivocal evidence of active pyelitis; yet in neither was there evidence of pyelonephritis, the inflammatory process not having involved the renal parenchyma. Their ages were 28 and 31 years respectively, so that a primary (essential) malignant hypertension is unlikely, and they raise the question as to what part pyelitis *per se*, without pyelonephritis, may play in initiating renal ischaemia and consequent hypertension. No definite conclusion can be drawn from the first case, since a unilateral nephrectomy was performed; functional tests had suggested that the other kidney was healthy, but pyelonephritis cannot of course be excluded, and may have been the cause of the hypertension. The blood-pressure remained high in spite of the nephrectomy.

A last difficulty in the differential diagnosis of chronic pyelonephritis has already been referred to. In cases of chronic renal failure in young subjects, often accompanied by so-called renal rickets, both kidneys are often very small, loss of nephrons is extreme, and some evidence of pyelitis may be present; in such cases the morphological data are often insufficient for a clear elucidation of the pathogenesis, the possibilities being at least three:

1. A late stage of slowly progressive Type 1 nephritis.
2. A late stage of chronic atrophic pyelonephritis.
3. Renal agenesis or hypoplasia complicated by pyelonephritis.

In view of the difficulties these cases have been relegated to a separate group.

Malignant Hypertension (24 cases)

Clinical features. The principle clinical criteria by which we have distinguished the malignant type of hypertension are three, namely, papilloedema, a very high diastolic blood-pressure, and the development of renal failure. Without the first two we never make the diagnosis, the third inevitably ensues unless the patient dies prematurely of cardiac or cerebral complications. The syndrome may occur as a variety or termination of essential hypertension, or it may be superimposed upon hypertension secondary to other causes such as nephritis, pyelonephritis, or periarteritis nodosa. The term malignant hypertension without qualification is used by us only to denote the malignant phase

of essential hypertension. When secondary cases of hypertension are strictly excluded it is found that malignant hypertension rarely occurs either in young or in old persons; most cases of so-called malignant hypertension in young persons turn out to be secondary to some pre-existing renal disease (Platt, 1948). The average age of death of our 24 cases was 47 years, the range being from 34 to 59 years. As malignant hypertension nearly always ends fatally within a year or two of the first symptoms, the age at which the patients were first seen would not be greatly different, though in a few cases there was a history of hypertension having been discovered, perhaps fortuitously, some years before.

In our opinion the clinical diagnosis of malignant (essential) hypertension should be made both on positive and negative features, namely, the absence of any history of pre-existing renal disease (including urinary infection), the fact that hypertension has preceded albuminuria and renal insufficiency (this is most clearly observed in those cases which have been followed from the benign to the malignant phase), the characteristic age incidence, and the family (usually parental) history of hypertensive disease (Platt, 1947). We are very reluctant to make a diagnosis of malignant hypertension in persons under 35 years of age or in any patient whose two parents are still living. Cases 4, 5, and 6 illustrate the pitfalls of making a diagnosis of malignant hypertension in these circumstances. All three had the features of malignant hypertension and would have been so diagnosed in most clinics. The first was found to have periarteritis nodosa, the second hydronephrosis, and the third pheochromocytoma. In making the diagnosis of the malignant phase of hypertension, evidence of papilloedema must be unequivocal, the cerebrospinal fluid pressure is generally raised and the fluid may contain excess of protein, and the diastolic blood-pressure, except in the terminal stages or during severe heart failure, is always 140 or more. In this series the range was 140 to 195. These features may all precede the onset of renal failure. Nevertheless, uraemia was present before death in all but three of our cases.

Pathological features. The naked-eye and histological features of the kidneys in malignant hypertension have been adequately described by Fahr (1919), Klemperer and Otani (1931), Kimmelstiel and Wilson (1936*b*), and Ellis (1942). In general the kidneys in our series were either enlarged or normal in size, rarely contracted, the weights ranging between 220 and 60 gm., with an average of 160 gm. The surfaces were either smooth or finely granular, and characteristically the cortex showed yellowish-red mottling which obscured the pattern (Plate 3, Fig. 4). The heart in all cases showed left ventricular hypertrophy, the weights ranging from 380 to 720 gm., with an average of 535 gm. Histologically the characteristic features of endarteritis fibrosa of the intralobular arteries and fibrinoid necrosis of arterioles and glomeruli were present in varying degrees. Glomerular lesions, necrosis or capsulitis, rarely involved more than 10 to 20 per cent. of the glomeruli, and the total number of glomeruli present was usually normal.

The diagnosis can usually be made correctly at autopsy. Left ventricular hypertrophy associated with kidneys scarcely if at all contracted, and showing

the characteristic reddish-yellow cortical mottling, points to the diagnosis of malignant hypertension. Atypical features in the history such as pyrexia, leucocytosis, rheumatic pains, etc., should arouse the suspicion of periarteritis nodosa and a careful search should be made for vascular nodules, especially on the coronary and mesenteric arteries, and numerous organs must be sectioned. Slowly progressive Type 1 nephritis is not difficult to exclude at autopsy; the

TABLE III

Secondary Hypertension of Malignant Type

Number of cases	*Diagnosis*	*Ages (years)*
4	Periarteritis nodosa	23, 26, 28, 34
2	Pyelonephritis	8, 48
2	Pyelitis	28, 31
3	Hydronephrosis	31, 33, 42
1	Renal tuberculosis	32
1	Pregnancy kidney	23
1	Pheochromocytoma	33

kidneys are usually grossly contracted, and histologically numbers of glomeruli have disappeared, many are fibrotic, and few are normal. The diagnosis from pyelonephritis has already been discussed. Rapidly progressive Type 1 nephritis may show similar naked-eye appearances, but histologically there is little or no vascular change, almost all glomeruli are affected, and the clinical course with oedema is characteristic. In addition to the 24 cases of primary malignant hypertension, there were 14 cases in which the renal lesion of malignant hypertension was present, but a primary cause for the hypertension was found. These are listed in Table III and described under their respective headings. The average age in these secondary cases was 29 years, with a range from eight to 48 years. We would emphasize the fact that in this total of 38 cases of hypertension of the malignant type, more than a third are secondary to renal or non-renal causes. In two cases of this type (Cases 7 and 8) not included in the above series, no satisfactory diagnosis was made. The first was probably an example of slowly progressive Type 1 nephritis with a malignant termination, but there was no history of a preceding attack of acute nephritis. In the second case the clinical history was suggestive of periarteritis nodosa, but we were not able to find the characteristic arterial lesions of that condition, except possibly in small arteries in the peripelvic tissue.

Benign Hypertension (16 cases)

The number of cases of benign hypertension gives no information as to its actual incidence in the period under review, as our cases were selected because renal disease had been suspected or diagnosed during life or at post-mortem examination. Most of them therefore showed more evidence of renal damage than is usually encountered in benign hypertension. We have divided them into three groups:

1. Benign hypertension with slight or moderate renal damage (10 cases).
2. Benign hypertension with severe renal damage (3 cases).

3. Cases which seem to be on the borderline between benign and malignant hypertension (3 cases).

The first group needs no discussion, but we would emphasize that a diagnosis of malignant hypertension cannot be made on the height of the blood-pressure alone. In one of these cases the blood-pressure was 260/180. As to the second group, Ellis (1942) stated that a small number of cases of benign hypertension progress to renal failure without developing the malignant phase. While we believe this to be true, and we have put three cases into that group, we are bound to admit that pathologically they are difficult to classify, since the loss of nephrons, the interstitial fibrosis, and the vascular sclerosis may suggest slowly progressive Type 1 nephritis or even healed pyelonephritis. Clinically also the diagnosis was in doubt in all three cases, although they all showed severe hypertension with renal failure and without papilloedema. One of them was complicated by leukaemia and had also had a urinary infection; the second gave a history of rheumatic fever and was later treated for rheumatoid arthritis, when albuminuria was found; and the third case had no history suggestive of chronic hypertensive disease. The last two are described briefly in the Appendix (Cases 9 and 10). We have also seen the syndrome of chronic hypertension with renal failure and without papilloedema in cases of periarteritis nodosa. In the third group the distinction between severe benign hypertension and the early malignant phase must sometimes remain a personal impression of the pathologist concerned, and dogmatic decision or precision cannot be achieved. It is, however, worth noting the close correlation between clinical and pathological impressions in this group, in which clinical data such as a very high diastolic blood-pressure, a raised blood-urea, or doubtful papilloedema suggested the commencement of the malignant phase.

Periarteritis Nodosa (15 cases)

The majority of the cases of periarteritis nodosa encountered in this 11-year period have already been the subject of a special communication (Davson, Ball, and Platt, 1948) and we have little further to add. We have since seen six more cases, three of the microscopic form without hypertension (Group A) and three associated with malignant hypertension, of which two were of the aneurysmal type (Group B) and the third was unusual in that perivascular fibrinoid lesions resembling tubercles were present. In all three cases with clinical malignant hypertension there were occlusive renal artery lesions due to periarteritis nodosa which could have been a primary cause of renal ischaemia and hence of secondary hypertension (Plate 4, Fig. 5).

Relation of periarteritis nodosa to malignant hypertension. We do not accept the extreme view, either on clinical or pathological grounds, that malignant hypertension is a manifestation of periarteritis nodosa (Moschcowitz, 1945–6). Elsewhere we have indicated the mechanism by which the ischaemic renal vascular lesions of periarteritis nodosa may initiate renal hypertension and the renal lesions of malignant hypertension may then be superimposed. Never-

theless Case 8 indicates that an absolute distinction between the two diseases cannot always be drawn successfully on clinical or pathological grounds.

Hydronephrosis (11 cases)

Eleven cases fall into this group, of which nine were seen at autopsy, and in two the kidneys were obtained by nephrectomy undertaken for the relief of hypertension. In one of these the blood-pressure was materially lowered by

TABLE IV

Hydronephrosis

Age (years)	*Sex*	*Hypertension*	*Uraemia*	*Pyelonephritis*	*Notes*
64	F	0	0	+	Died of diabetes.
39	M	+	0	+	Nephrectomy.
31	M	+	+	0	Unilateral.*
44	F	0	+	+	Bilateral.
29	M	+	0	+	Nephrectomy.
22	M	+	+	+	Bilateral.
42	M	+	+	0	Unilateral.*
33	M	+	+	0	Unilateral.*
58	F	+	+	0	Bilateral.
46	M	+	+	+	Unilateral.
62	F	0	+	+	Unilateral.

* Malignant nephrosclerosis in opposite kidney.

the operation, but not to normal. Of the autopsy cases there were three with bilateral hydronephrosis, and three with hydronephrosis in one kidney and pyelonephritis in the opposite kidney. Three further cases were of special interest, since unilateral hydronephrosis was present and the other kidney showed only the changes of malignant nephrosclerosis (Plate 4, Fig. 6). Although no absolute conclusion can be drawn from autopsy material, the occurrence of these cases appears to support the view that malignant nephrosclerosis may arise as a result of unilateral renal disease. Case 5 illustrates this occurrence. Table IV gives brief particulars of the 11 cases of hydronephrosis, and it appears that hydronephrosis can occasionally be a cause of severe hypertension, even though uncomplicated by pyelonephritis. The eight cases complicated by uraemia form part of a large group of patients whom the clinician often sees for the first time when their disease is already far advanced. Intravenous pyelograms are of no assistance, as the kidneys at this stage are unable to concentrate diodrast. Retrograde pyelography hardly seems justifiable, as the information obtained can only be of academic interest and a fatal urinary infection can easily be precipitated. Those who are ignorant of the multiple causes of renal failure will make a diagnosis of chronic nephritis or of malignant hypertension, but we prefer to describe them simply as renal failure from a clinical point of view until pathological evidence can be obtained. The correct diagnosis can sometimes be suspected or made by the history, or by palpation of the kidneys.

Diabetic Glomerulosclerosis (9 cases)

Clinical features. The fully developed syndrome of diabetic glomerulosclerosis, with gross albuminuria, general oedema, hypoproteinaemia, hypertension,

retinopathy, and renal failure, is indistinguishable clinically from severe Type 2 nephritis, except for the presence of the pre-existing diabetic state, and for the fundus oculi which often shows a mixture of the hypertensive and diabetic types of retinopathy. There are cases, however, in which oedema does not occur, and in our experience the presence of heavy albuminuria with deteriorating renal function in a diabetic of some years' standing is sufficient to establish the diagnosis, and to predict with considerable assurance the finding of the

TABLE V

Diabetic Glomerulosclerosis

Age (years)	*Sex*	*Duration of diabetes (years)*	*Blood-pressure*	*Blood-urea (mg. per 100 c.c.)*	*Oedema*	*Albumin-uria*	*Confirmed histo-logically*	*Serum-proteins albumin/ globulin (gm. per 100 c.c.)*
Living								
40	F	16	200/130	150	..	++	..	..
42	M	24	200/120	34	+	+	..	..
39	M	18	170/110	120	+	+	..	..
59	F	16	235/110	50	+	+	..	2·7/2·9
48	M	14	200/115	56	+	+	..	3·5/2·4
57	M	18	190/110	120	++	++	..	3·1/2·6
33	F	18	200/115	44	+	++	..	3·4/2·4
Dead								
69	F	10	140/90	22	++	++	Yes	..
61	F	?	180/70	..	+	++	Yes	..
56	M	8+	210/130	180	..	++	Yes	..
47	F	?	130/85	..	+	+	Yes	..
42	F	9	180/110	162	++	++	Yes	3·3/2·6
59	F	2	280/130	310	+	++	Yes	..
58	F	3	190/110	290	++	++	Yes	3·7/2·5
58	F	8	135/75	..	++	+	Yes	..
31	F	21	140/95	84	++	++	Yes	..

typical lesions described by Kimmelstiel and Wilson (1936*c*). This is in accord with the description of Laipply, Eitzen, and Dutra (1944) and Rifkin, Parker, Polin, Berkman, and Spiro (1948). In eight of our nine fatal cases the diagnosis was correctly made during life or from reading the case notes. In the remaining one the clinical data were inadequate. It is important to realize that the syndrome can be present in young persons, though they have usually had diabetes for many years. Table V gives the age incidence and duration of the diabetes in 16 cases, nine of which have been proved by post-mortem examination. It will be noted that the youngest patient, aged 31 years, in whom the lesion has been found, had had diabetes for 21 years.

We cannot as yet offer any helpful observations upon aetiology or treatment, but we would point out that the condition occurs both in the young, acute, severe diabetic and in the elderly, obese, chronic type. If it be true that these types of diabetes are of different aetiology, then the glomerulosclerosis must be produced not by the aetiological factor of diabetes, but by some change consequent upon the diabetic state. We cannot be sure that the renal disorder is more likely to occur in those diabetics who have been careless in their régime. In only one case was the diagnosis made from histological examination where

clinical diabetes was not known to be present, and it is interesting and possibly significant that in that case the pathologist noted chronic atrophic fibrotic changes in the pancreas. The patient was a man of 65 years admitted with albuminuria and heart failure. One urine test only was made and reported to be negative for sugar. He was not seen by us during life and is not included in the 16 cases listed in Table V. Data on serum-proteins are lacking from many of the records, but in the cases which we have had under personal observation there is in general an inverse relation between serum-albumin and oedema, similar to that found in Type 2 nephritis.

Pathological considerations. Kimmelstiel and Wilson (1936c) first pointed out that the kidneys in some cases of diabetes show characteristic glomerular lesions, and subsequently Laipply, Eitzen, and Dutra (1944), Herbut (1941), Allen (1941), and others have confirmed the fact and added more detailed histological descriptions. In our series there were nine cases in which the typical lesions were present histologically. The kidneys showed no consistent naked-eye appearances that could be regarded as characteristic of the condition. In three apparently early cases they were somewhat enlarged, weighing between 200 and 280 gm., the surfaces were smooth, and no obvious disturbance of architecture was visible. In the remaining cases slight to moderate degrees of granularity of the surface were present, and several showed loss of cortical pattern and cortical thinning. In the latter cases the histological lesions were advanced and widespread. In general it appears that gross contraction does not occur in this condition. In seven of Herbut's nine cases the kidneys were enlarged. Histologically the diagnosis was made by the finding of the typical Kimmelstiel–Wilson bodies in the glomeruli (Plate 4, Fig. 7), round or oval hyaline masses which stain variably pale pink or bright red in sections stained by haemalum and eosin, red or green with Masson's stain, and usually bright red with Heidenhain's azan stain. In the more severe cases, many glomeruli were completely filled by these masses while others appeared more homogeneously hyalinized, and the latter gave the usual collagen staining—green with Masson and blue with Heidenhain's azan. In the early cases only an occasional glomerulus showed the typical lesions, and the tubules showed little abnormality. In the severe cases the tubules were mainly atrophic and intertubular fibrosis and round cell infiltration were widespread. Hyaline changes in the arterioles were present in varying degrees in all the cases, but the amount showed no close relation to the presence or absence of hypertension during life. In some cases the staining reaction of the arteriolar hyaline material was more eosinophilic than in non-diabetic nephrosclerosis, resembling the staining reaction of some of the Kimmelstiel–Wilson bodies and suggesting that it had been produced by the same process. It may therefore be of a different nature from the hyaline arteriolar sclerosis of hypertension and may explain the comparative lack of correlation between arteriolar lesions and clinical hypertension in these cases. Allen (1941) commented on the disparity between the often widespread and severe arteriolosclerosis and the absence of a comparable degree of contraction on naked-eye examination. This further suggests that the

arteriolosclerotic vessels are not identical with those of hypertensive arteriolosclerosis. On the other hand Rifkin, Parker, Polin, Berkman, and Spiro (1948) found that arteriolar lesions were closely related to the presence of hypertension. One morphological characteristic may be mentioned. Even when the glomeruli are completely hyalinized, they do not appear to shrink or disappear as in most other nephropathies, but remain as distinct, even enlarged, hyaline balls even in the advanced stages, so that a distinctive picture may be presented of a field filled with large hyaline glomeruli separated by scanty and atrophic tubules (Plate 4, Fig. 8). The deposition of hyaline material may be diffuse within the glomerulus as well as focal. In such glomeruli the resemblance to the intercapillary hyaline change in the intermediate and later phases of Type 2 nephritis may be close.

Specificity of Kimmelstiel–Wilson lesions. Laipply, Eitzen, and Dutra (1944) concluded that intercapillary glomerulosclerosis has a close correlation with diabetes. Our findings confirm this view. Clinical diabetes was proved in eight of the nine cases which showed these lesions. In a tenth case, already mentioned as excluded from this group, ischaemic fibrotic changes in the pancreas were present, indicating the likelihood of senile diabetes.

Differential diagnosis. The late stage of Type 2 nephritis in which many glomeruli are almost completely hyalinized may resemble the late stage of diabetic glomerulosclerosis, but in the latter the typical oval eosinophilic Kimmelstiel–Wilson bodies can usually still be recognized in a number of the glomeruli. In amyloid disease of the kidney the deposits do not take the circumscribed round or oval shapes of the Kimmelstiel–Wilson bodies; and the latter do not give a positive amyloid stain.

Renal Hypoplasia (9 cases)

We have already said that in cases where one or both kidneys are very small it may be extremely difficult to decide whether there is primary hypoplasia, or whether the contracted state represents the late stage of slowly progressive Type 1 nephritis or of chronic atrophic pyelonephritis. Such kidneys show few remaining glomeruli, and often large fields of dilated hypertrophic tubules; the position is made no easier by the fact that pyelonephritis is a very common complication of hypoplastic kidney. There were four female patients aged 8, 32, 52, and 60 years respectively in whom the renal hypoplasia was unilateral. In three of these nephrectomy was performed because severe hypertension was found, with a normally functioning kidney on one side and a non-functioning kidney on the other. Two of these cases have already been reported (Langley and Platt, 1947, Cases 1 and 8). In one the operation was a complete cure, in the others it was unsuccessful in relieving the hypertension. In each case the kidney, although small, had a relatively smooth surface and did not appear to be grossly contracted (Plate 5, Fig. 9). In one, only three medullary pyramids were visible (Plate 5, Fig. 10). For these reasons a diagnosis of renal hypoplasia was made despite a superimposed chronic pyelonephritis. In the fourth unilateral case a very small kidney weighing only 10 gm. was found at autopsy;

the patient had died of malaena, and had not shown renal failure or hypertension during life. There was one case of apparent bilateral renal hypoplasia, a man aged 39 years with hypertension and renal failure. At autopsy two small coarsely granular kidneys weighing 20 and 40 gm. were found. Histologically there was evidence of gross loss of nephrons, a few glomeruli lying in fields of dilated tubules, and it was difficult to say whether this was a primary renal hypoplasia or a bilateral chronic atrophic pyelonephritis. This case has also been reported (Platt, 1948). There were four other patients, aged 18, 17, 24, and 25 years, of whom two showed the clinical features of renal dwarfism, and all showed a chronic uraemic state of obscure origin. In all four cases both kidneys were very small and granular, and the histological picture was that of a few surviving glomeruli lying in fields of dilated tubules. It was not possible to decide between renal hypoplasia and chronic atrophic pyelonephritis as the cause. Slowly progressive Type 1 nephritis in the late stage was improbable, since gross hypertension and cardiac hypertrophy were not present.

This group therefore comprises cases with very small kidneys on one or both sides; in some the existence of hypoplasia is indicated by the lack of evidence of fibrotic contraction, or abnormally few pyramids; in others no definite conclusion can be reached. As renal dwarfism is usually the result of a very slowly progressive insufficiency which has its origin at birth or in early infancy, this type of kidney is often seen. In other cases the cause is bilateral hydronephrosis (Ellis and Evans, 1933).

The Kidney of Dehydration and Anoxia (10 cases)

In this heterogeneous group there has usually been a clinical state of acute extrarenal uraemia due to diabetic coma or haemorrhage. At autopsy enlarged pale kidneys have been found, and histologically the chief lesion has been dilatation of the convoluted tubules with atrophy of their epithelium (Plate 5, Fig. 11), resembling the tubular changes in Type 2 nephritis. No glomerular lesions are found, and the condition is regarded as secondary either to dehydration or to anoxia (Maegraith, Havard, and Parsons, 1945). The precipitating cause of the renal lesion was diabetic coma in five cases, haemorrhage in one, diarrhoea in one, severe anaemia in two, and heart failure in one. The number of cases gives no indication of the absolute incidence of such conditions, but merely represents those instances in which, owing to clinical or pathological findings, the question of renal damage was investigated.

Pregnancy Kidney (2 cases)

We have, unfortunately, been unable to study the kidney of pregnancy toxaemia during the acute stage, and our two instances are both patients in whom a permanent, severe, and fatal hypertension developed after one or more pregnancies complicated by pre-eclamptic toxaemia. On clinical grounds we have no doubt of the occurrence of these cases and of their severity, for we have seen persistent hypertension develop in women whose blood-pressure was known to have been normal at the commencement of the toxaemic pregnancy;

and they have neither the age incidence nor the family history of essential hypertension. Pathologically, however, the kidneys at this stage are apparently indistinguishable from primary essential hypertension either of the benign or of the malignant type, and do not require separate description.

Rarer Renal Lesions

We propose to refer very briefly to some of the rarer types of renal disease which we have encountered in this survey, not because they are lacking in interest, but because from our small experience of them we have little to add to the literature already published.

Amyloid disease (*3 cases*). In the early stages the amyloid kidney usually presents a clinical picture almost indistinguishable from that of Type 2 nephritis. In other words it is oedema of which the patient complains, and this leads to the testing of the urine and the finding of a heavy albuminuria. In our experience it is rare to find a palpable liver or spleen at the commencement of these symptoms, and the true diagnosis is suggested only by the fact that the syndrome is superimposed upon chronic sepsis or tuberculosis. It is important to make the diagnosis early, as the condition may clear up if the underlying disease can be radically treated. Later on renal failure and often hypertension develop. Two of our cases followed upon bronchiectasis and pulmonary tuberculosis respectively. Both patients had uraemia with a normal blood-pressure; one was unusual in having had no oedema. Our third case was one of so-called primary atypical amyloidosis, and is described in the Appendix as Case 11. The histological diagnosis is made by the usual staining methods for amyloid material, and the differential diagnosis has been discussed under Type 2 nephritis in the first part of this study (Davson and Platt, 1949).

Multiple myelomatosis (*3 cases*). It is well known that multiple myelomatosis may lead to renal failure, and the combination of severe anaemia with proteinuria and uraemia, especially in an elderly subject, should arouse suspicion. None of the three patients was seen by us during life, and all were admitted *in extremis*, the diagnosis being made only at autopsy. We cannot therefore say whether the Bence-Jones proteose was present in the urine. Histologically the diagnostic lesion is the presence of very large numbers of eosinophilic casts in the convoluted tubules (Plate 5, Fig. 12).

Disseminated lupus erythematosus (*2 cases*). These two cases, both of which occurred in young women, ran the typical clinical course with episodes of pyrexia, joint pains, pleural effusion, and pericarditis. Both had the typical rash, and both showed albuminuria. One died of hypertension and renal failure; the other had a normal blood-pressure, and good renal function was maintained until the end. In both cases histological examination showed the characteristic lesions of the glomeruli (Plate 6, Fig. 13). Pathologically these cases may resemble Type 2 nephritis, and the diagnosis has already been discussed in Part I of this investigation (Davson and Platt, 1949). As a rule the clinical history leaves one in no doubt.

Pheochromocytoma (*1 case*). This patient, a man of 33 years, has already been referred to in discussing the diagnosis of malignant hypertension, and is described fully in the Appendix (Case 6). During the time that he was in hospital, when the disease was well advanced, the hypertension was fixed and not paroxysmal. At the autopsy bilateral tumours were found in the adrenals (Plate 6, Fig. 14). The kidneys were indistinguishable from those of malignant hypertension, but we believe that in this type of case the renal lesion is secondary to the high blood-pressure.

Renal tuberculosis with hypertension and uraemia (*1 case*). Patients with renal tuberculosis frequently die of uraemia when bilateral destruction of the kidneys is far advanced. In a few cases the sequence of events is different; the tuberculous lesion appears to lead to the development of hypertension, presumably through renal ischaemia, and this if sufficiently severe induces the secondary changes of malignant nephrosclerosis, with renal failure. Our patient was a man of 32 years, not seen by us during life. The clinical picture was that of hypertension with papilloedema. The blood-pressure was 250/160, and the blood-urea before death was 400 mg. per 100 c.c. Post-mortem examination showed tuberculous pyonephrosis of one kidney, while the other showed the characteristic changes of malignant nephrosclerosis with a small caseous focus in the upper pole. This case can be compared with Case 5, in which hydronephrosis gave rise to hypertensive changes in the opposite kidney.

Scleroderma (*1 case*). This patient was a woman of 40 years, whose final illness was heart failure with hypertension and uraemia. She was not seen by us during life. There was oedema of the legs, orthopnoea, and albuminuria. The blood-urea was 154 mg. per 100 c.c.; the urea clearance was 11 per cent. of normal. There was scleroderma of the face and hands with pigmentation. Previous records showed that she had been treated for this condition for more than three years.

At post-mortem examination each kidney weighed 100 gm. The renal surfaces were smooth but mottled. Histologically the main renal lesion was endarteritis fibrosa of the intralobular arteries, but microscopic infarcts and necrotizing vascular lesions of the periarteritis nodosa type were also seen. The relationship of scleroderma to periarteritis nodosa has been discussed by Banks (1941), who described a similar case.

Unclassified Cases

We are left with seven cases to account for, in which we have not been able to come to a satisfactory diagnosis: a failure of less than 4 per cent. in the whole series, despite the fact that in many cases the notes alone were available for making a clinical diagnosis. Two of these cases have already been mentioned at the end of the section on malignant hypertension, and are described as Cases 7 and 8. Two more we believe on clinical and pathological grounds to be periarteritis nodosa, but have been unable to confirm the diagnosis by finding typical arterial lesions. One patient had a clinical history typical of Type 2 nephritis, but the histological picture was unusual and showed partial

calcification of tubules. One case, which showed the Kimmelstiel–Wilson lesion without known clinical evidence of diabetes, has already been referred to. The remaining case is one in which extensive patchy cortical necrosis was found in the kidney of a young woman who died of bilateral adrenal haemorrhage.

Summary and Conclusions

In previous papers we have discussed the Ellis classification of nephritis, the clinical and pathological diagnosis of Type 1 and Type 2 nephritis, and the renal lesions of periarteritis nodosa. The present paper gives a more general survey of fatal cases of renal disease, in an attempt to show that an accurate diagnosis can be arrived at in the majority of cases on clinical grounds alone, and in nearly all cases by careful clinical and pathological collaboration.

Although the diagnosis of renal disease has been considered difficult or unsatisfactory in the past, we claim to be able to come to a conclusion satisfactory to clinician and pathologist in about 95 per cent. of cases. This has, we feel, more than an academic importance, for it indicates the approach to a better understanding of the pathogenesis and prognosis, in fact of what Ellis has called the natural history of Bright's Disease. Without a rational classification, study of the fundamental processes of disease is impossible.

We particularly call attention to Table I, which shows the statistical distribution of our 188 cases of renal disease, and gives the relative frequency of the various causes of renal failure which have been encountered in this series. We have been specially interested in the differential diagnosis of the patient who is first seen by the physician in a late stage of renal disease, when uraemia and usually hypertension are already far advanced. We suggest that the term 'renal failure' or 'renal failure with hypertension' should be used for this type of case, simply to describe the syndrome without reference to aetiology, thus avoiding undesirable and meaningless terms like chronic interstitial nephritis. Nevertheless a more accurate diagnosis should be aimed at wherever possible, and in making this the clinician will be chiefly aided by two things. The first is a knowledge of the numerous causes of this syndrome as presented in our table, with a full realization of the importance of pyelonephritis, periarteritis nodosa, congenital defects, and so-called surgical disorders as causes of renal failure. The second major factor in arriving at an accurate diagnosis will be the taking of a careful history, with particular emphasis upon previous episodes of ill health. When renal failure is seen only in its terminal stage, examination and laboratory investigation will allow a nice assessment of the severity of the disease, but will rarely assist materially in the diagnosis of its cause.

Finally we would again plead for a correct use of the term malignant hypertension. If, as we hold, there is no longer any meaning in the label chronic interstitial nephritis still used by the older physicians, the indiscriminate use of the term malignant hypertension by their younger colleagues, to include almost any case of terminal hypertensive disease with renal failure, discloses equal ignorance with less excuse.

We are grateful to our colleagues at the Manchester Royal Infirmary for permission to use their case records, and specially to Professor T. H. Oliver, through whose kindness we have seen most of the cases of diabetic glomerulosclerosis.

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APPENDIX

Three Cases illustrating Chronic Atrophic Pyelonephritis of the Uraemic, the Hypertensive, and the Mixed Types

Case 1. A man aged 54 years was seen in the Out-patient Department in January 1948. He complained merely that he felt tired, run down, and weak, and that these symptoms had been increasing in severity for the previous three years. Lately his appetite had been poor and he had lost 10 lb. in weight. Occasionally he had cramp in his legs, and he had had epistaxis two months before. He looked ill and anaemic, but had no notable physical signs; the blood-pressure was 140/90. The blood count showed red cells 2,970,000 per c.mm., haemoglobin 58 per cent., colour index 0·98, and white cells 5,800 per c.mm. (it was noticed later that this count shows the typical normochromic anaemia of renal failure). He was admitted for investigation and it was found that he had constant albuminuria. The blood-urea was 340 mg. per 100 c.c., and later rose to 430 mg. per 100 c.c. The urine contained 0·5 gm. of albumin per litre, and on culture there was a light growth of a coliform organism. Other tests were consistent with the serious uraemic condition. There was no previous history of nephritis, and he was therefore carefully questioned for evidence of

previous attacks of urinary infection, and he admitted that on a number of occasions he had experienced what he called a chill, which was associated with some urinary frequency and occasionally a little scalding on micturition. On this evidence and in the absence of any other cause of uraemia it was considered likely, though by no means certain, that chronic pyelonephritis was the cause of his illness.

Post-mortem examination showed small, coarsely scarred, contracted kidneys weighing 90 and 35 gm. respectively. Both showed gross atrophy of the cortex. Histologically the left kidney showed severe atrophic healed pyelonephritis. In the right kidney there was still some activity of the pyelonephritic process. The vessels showed severe intimal sclerosis, especially in the left kidney.

Case 2. A woman aged 37 years was admitted in April 1947 on account of shortness of breath, headache, and pain in the chest on exertion. The only previous history of importance was that she had had attacks of pyelitis in two pregnancies, 13 and 14 years before. Since then there had been no symptoms until the gradual onset of shortness of breath a few months before admission. There was no family history of hypertensive disease, and both her parents were alive. On examination the blood-pressure was 240/150, but there was no papilloedema. Tests of renal function were satisfactory, the maximum specific gravity of the urine being 1,030, and the blood-urea 36 mg. per 100 c.c. An intravenous pyelogram showed what was apparently a normal kidney on the left side, but a poorly functioning kidney on the right side with deformed calyces. Cultures of the urine were sterile and it contained usually only a trace of albumin, sometimes none at all.

The right kidney was removed in April 1947. It showed gross irregularity of surface with a pale cortex of variable thickness. Histologically chronic atrophic pyelonephritis was present, with evidence of hypertension. The blood-pressure in June 1947 was 175/110 and in July 195/115.

Case 3. A woman aged 31 years was admitted to hospital in June 1946 complaining of breathlessness, weakness, and headache. She said that she frequently had pains in the loins and had recently had blood in the urine, that at the age of seven years she had had inflammation of the bladder, and that she had had a number of similar attacks since that time. She had had four pregnancies. During the first and third pregnancy it was noted that albumin was present in the urine, and the fourth pregnancy was terminated on account of high blood-pressure. There was no family history of hypertension, and her father and mother were alive and well. On examination the blood-pressure was 205/130, and it was obvious that she was in a terminal condition of cardiac and renal failure. The blood-urea was 296 and rose to 394 mg. per 100 c.c. before she died. The urine showed albumin constantly and contained some pus cells. Culture showed a gram-negative bacillus. A diagnosis of chronic atrophic pyelonephritis was made with some confidence. There was nothing to suggest that she had had a true pregnancy toxaemia.

Post-mortem examination showed the typical appearances of chronic atrophic pyelonephritis with two irregularly contracted kidneys weighing 34 and 120 gm. respectively. There were necrotic lesions of malignant nephrosclerosis in some of the glomeruli; others were reduced to small hyaline or fibrous nodules. There were many dilated tubules containing large hyaline casts and giving the typical 'thyroid' appearance. The interstitial tissue was infiltrated with lymphocytes, and the pelvis of each kidney showed chronic inflammatory changes. The bladder showed a chronic cystitis.

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Three Cases illustrating Pitfalls in the Diagnosis of Malignant Hypertension

Case 4. A man of 26 years developed continuous frontal headache in February 1946. This was followed by colicky pain in the right side of the abdomen, and he stated that he could feel a lump in the right lumbar region. A few weeks later his vision became blurred and attacks of vomiting developed. There was no previous history of importance, and no family history of renal disease or hypertension. He was transferred to our care from another hospital with a diagnosis of malignant hypertension. The blood-pressure on admission was 215/160. There was bilateral papilloedema with exudates. The urine contained 3 gm. of albumin per litre. His general condition rapidly deteriorated and his blood-urea rose to 220 mg. per 100 c.c. before death. We were reluctant to accept the diagnosis of malignant hypertension because of the rarity of essential hypertension at this age, the absence of family history, the finding of a slight, inconstant pyrexia, the history of abdominal pain, and a leucocytosis on one occasion of 19,500 per c.mm. A tentative diagnosis of periarteritis nodosa was made, but a biopsy was negative. Post-mortem examination, however, showed typical macroscopic appearances of periarteritis nodosa with small aneurysms on the coronary, mesenteric, hepatic, and renal arteries, and elsewhere.

Case 5. A man aged 31 years was admitted to hospital in January 1947 complaining of pain in the right lumbar region, haematuria, and headache. He had suffered from increasing periodic headache for about two years, and had noticed blurring of vision a few days before his admission to hospital. Recently there had been some shortness of breath on exertion, aching pain in the right loin had been present for some weeks, and haematuria for a few days. The family history was conspicuously free from hypertension; the two parents aged 78 and 73 years were living, as well as nine elder siblings. One brother had been killed in a motor accident. The blood-pressure on admission was 210/140; there was papilloedema with exudates. The heart was enlarged. Neither kidney was palpable. The blood-urea was 120, and rose to 494 mg. per 100 c.c. before death. The obvious diagnosis of malignant hypertension was not acceptable to us because of the age of the patient and his negative family history. On account of the pain in the loin, and haematuria, it was thought possible that a urological lesion would be found.

Post-mortem examination showed a large hydronephrosis on the right side, and in the left kidney the changes associated with malignant hypertension. We are bound to accept the view that severe hypertension of malignant type may be caused in the human subject by unilateral renal disease, as a few cases have been known to have been cured by nephrectomy. It is therefore reasonable to presume that the changes in the left kidney in this case were secondary to the hypertension.

Case 6. A man of 33 years was admitted under our care in September 1947. A few weeks before admission he had had an attack of hemiparesis on the right side which lasted for a few days. A few days before admission he had noticed blurring of vision, first in the left eye and later in the right. He stated that for about five years he had had thirst, polyuria, and nocturnal frequency, but there was no history of dysuria at any time, and no history suggesting nephritis. He had noticed some shortness of breath on exertion in the previous few months, but there was no history of attacks of severe headache or palpitation. His father and mother were both alive and well, aged 73 and 74 years. One brother and sister were well; one brother died suddenly at the age of 40 years.

The blood-pressure on admission was 270/170 and the lowest diastolic pressure recorded was 155, until the day before he died, when it was 120. There was bilateral papilloedema with exudates, haemorrhages, and retinal detachment on both sides. The heart was enlarged with a presystolic gallop rhythm. The urine contained blood and albumin. The blood-urea was 100 mg. per 100 c.c., rising to 480 mg. per 100 c.c. The case would have passed for one of malignant hypertension but for the age and the negative family history.

Post-mortem examination showed hypertrophy of the left ventricle. The kidneys weighed 150 and 160 gm. respectively, and showed the naked-eye and microscopic characteristics of malignant nephrosclerosis. The left adrenal gland weighed 55 gm. and contained a central bluish-red tumour measuring 6 by 3 cm. The right adrenal contained a similar tumour 1·5 cm. in diameter. Sections showed the tumours to be typical of pheochromocytoma.

Two Unusual Cases of Hypertension of Malignant Type

Case 7. A young woman aged 20 years had suffered from lassitude, loss of weight, and frontal headache for about nine months. Ten days before admission her vision had become misty and indistinct in both eyes. There was no previous history of renal disease or of urinary infection, but since the age of seven years she had had a chronic cough and also a discharging ear. At the age of four years she had had pneumonia, followed by an empyema which discharged intermittently for the next five years. On examination the main findings were a blood-pressure of 260/150, râles at the lung bases, bilateral retinopathy with a macular star on the right side, and atrophy of the left disk. The blood-urea was 106 mg. per 100 c.c., and the urea clearance 10 per cent. of normal. Death was due to cerebral haemorrhage.

Post-mortem examination showed contracted kidneys weighing 50 and 40 gm. Histologically numbers of glomeruli had disappeared, others were fibrotic, and there was fibrotic disorganization of the parenchyma, but the characteristic lesions of malignant nephrosclerosis were also to be seen. The pathological picture would be compatible with slowly progressive Type 1 nephritis on which a malignant termination had supervened.

Case 8. A woman aged 41 years had suffered from periodic attacks of feverish illness, associated often with headache and vomiting, and sometimes with redness and swelling of the face. This had been sometimes on the right side and sometimes on the left, and on more than one occasion there had been patches of reddish discoloration on the upper arms. In hospital her blood-pressure was 250/150, there was bilateral papilloedema, with exudates and haemorrhages, swelling and discoloration of the right cheek, and on one occasion some small nodules were felt in the arm. She was pyrexial throughout, and had a leucocytosis of 18,000 per c.mm. on one occasion. The urine contained albumin, but the specific gravity was 1,030. The blood-urea was 30 mg. per 100 c.c., and the urea clearance 98 per cent. of normal. She died from the cerebral complications of her hypertension.

Post-mortem examination showed oedema of the brain, small apparently rheumatic vegetations on the aortic and mitral valves, cardiac hypertrophy, acute colitis, and cholecystitis. The kidneys each weighed 120 gm. The renal lesions were those of malignant hypertension, and no typical lesions of periarteritis nodosa were found, in spite of a careful examination which included sections of the heart, kidneys, and aorta. A few necrotizing lesions were found in small arteries in the peripelvic tissue.

Two Cases illustrating Benign Essential Hypertension with Severe Renal Damage

Case 9. A man of 58 years was admitted to the Royal Infirmary, Manchester, in July 1946. Ten years before he had had rheumatic fever, and one year before, when he was treated for rheumatoid arthritis, albuminuria had been found. For eight months he had had occasional attacks of nocturnal dyspnoea, and for two months he had had swelling of the ankles spreading later to the legs. His mother died of apoplexy at 78 years, and his father of 'Bright's disease' at 48 years. One brother and one sister were alive and well. His clinical state was typical of hypertensive heart failure with pulmonary congestion, oedema of the legs and sacrum, and orthopnoea. There was considerable arteriosclerosis. The blood-pressure was 270/140. There was no papilloedema, but there was a small haemorrhage in the left retina. The urine contained albumin, and had a maximum specific gravity of 1,012. The blood-urea was 252 mg. per 100 c.c., and the urea clearance 5 per cent. of normal.

Post-mortem examination showed cardiac hypertrophy; the kidneys weighed 60 and 80 gm. respectively, both being small and congested, with narrow cortex and loss of striations. Microscopically a very few surviving glomeruli appeared normal. A number had completely disappeared; most showed hyaline and granular necrotic change of apparently recent origin. Groups of convoluted tubules were dilated with atrophic and degenerated epithelium. Many tubules had disappeared, being replaced by fibrous tissue. The larger arteries showed elastosis and obliterative endarteritis fibrosa. The arterioles showed severe hyaline changes, but without necrosis.

Case 10. A man aged 51 years was admitted under our care in October 1947. Six weeks before admission he had had an attack of what he described as dizziness while driving his car. This was the first symptom, and hypertension was then discovered. Since that time he had had some headache and occasional vomiting. There had been no previous history of illness of any kind. Both his parents died at about the age of 56 years, but he did not know the cause in either case. During his stay in hospital the blood-pressure varied from 200/130 to 230/145. There were a few small retinal haemorrhages, but no papilloedema. The urine contained from 0·5 to 1·5 gm. of protein per litre, and its maximum specific gravity was 1,010. The blood-urea was 180 mg. per 100 c.c. on admission, and rose to 356 mg. per 100 c.c. before death. Clinically this was a case in which there was no clue as to the cause of the hypertension and renal failure, and no diagnosis was made.

Post-mortem examination showed gross cardiac enlargement, the heart weighing 700 gm. The kidneys both weighed 75 gm. and showed a uniformly granular surface with a thick cortex. There was no evidence of pyelitis. Microscopically the appearances were similar to those in Case 9; there were severe hypertensive changes without arteriolar necrosis. Endarteritis fibrosa of the intralobular arteries was severe, hyaline arteriolosclerosis was marked, and numbers of glomeruli were completely fibrotic.

A Case of Primary Atypical Amyloidosis

Case 11. A woman aged 60 years complained of gradually increasing weakness and tiredness, which had been coming on for 18 months. Lately she had lost weight and appetite, and had developed shortness of breath on exertion and swelling of the legs. She had had occasional attacks of diarrhoea. It was

said that she had lately become mentally slow and that her voice had changed. Her doctor had treated her for anaemia. Examination in the Manchester Royal Infirmary showed that she was very wasted and lethargic; the skin was dry, scaly, and inelastic. She was not very co-operative. The tongue was smooth and atrophic. The blood-pressure was 150/100. The heart was enlarged; there was oedema of the legs, back, abdominal wall, and hands; there were a few râles in the chest; the liver and spleen were enlarged. The urine contained albumin. The blood count showed red cells 4,630,000 per c.mm., haemoglobin 90 per cent., colour index 0·97, and white cells 10,100 per c.mm. The serum albumin was 3·1 and serum globulin 2·8 per cent. The blood-urea was 180 mg. per 100 c.c., and rose to 232 before she died, apparently of uraemia, in a comatose state.

The case was not seen by us during life. The generalized oedema, uraemia, and splenic and hepatic enlargement would suggest amyloid disease, but there was no history of a long-standing infection to cause such a condition. Post-mortem examination showed hypertrophy of both ventricles of the heart, enlargement of the spleen (weight 750 gm.), and finely granular kidneys (weights 150 and 85 gm.) showing loss of cortical pattern and yellow lipoid deposition in the boundary zone. Histologically amyloid change was present in the liver, spleen, lung, thyroid, adrenals, kidneys, pancreas, myocardium, and aorta.

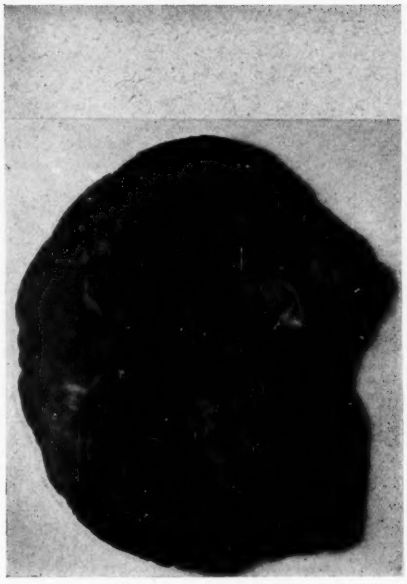

FIG. 1. Chronic atrophic pyelonephritis. A granular kidney with a few coarse scars. Natural size

FIG. 2. Chronic atrophic pyelonephritis. The coarse scarring is well shown. Natural size

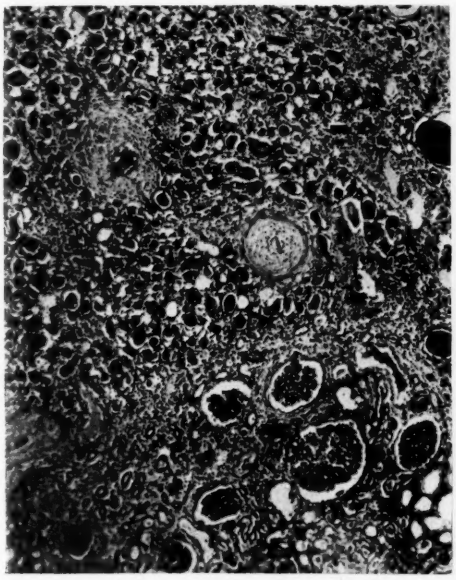

FIG. 3. Chronic atrophic pyelonephritis. Thyroid-like areas of tubules containing 'colloid' casts in the renal cortex (haemalum and eosin, ×50)

FIG. 4. Malignant hypertension. The kidney is but slightly contracted and the characteristic cortical mottling is well seen in the lower half. Natural size

FIG. 5. Periarteritis nodosa. Scattered cortical infarcts are present and the affected arcuate arteries show as prominent white foci. Reduced to 4/5ths natural size

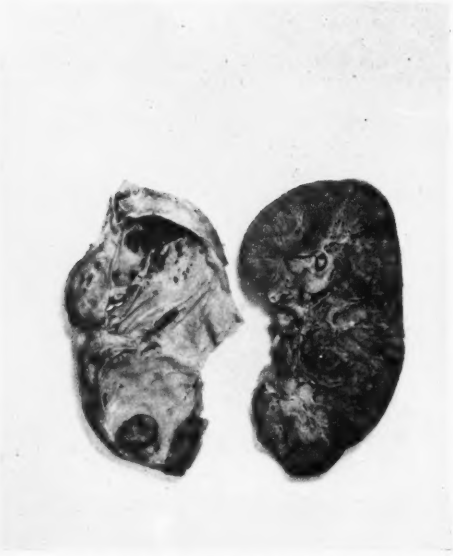

FIG. 6. Unilateral hydronephrosis with contralateral malignant nephrosclerosis. Reduced to 1/3rd natural size (Case 5)

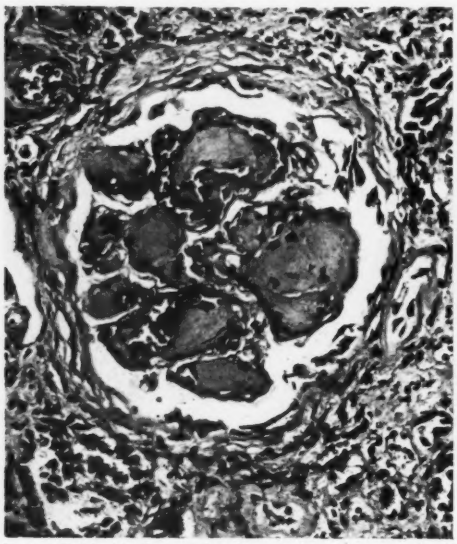

FIG. 7. Diabetic glomerulosclerosis. Numerous typical Kimmelstiel-Wilson bodies can be seen in the glomerulus (haemalum and eosin, ×225)

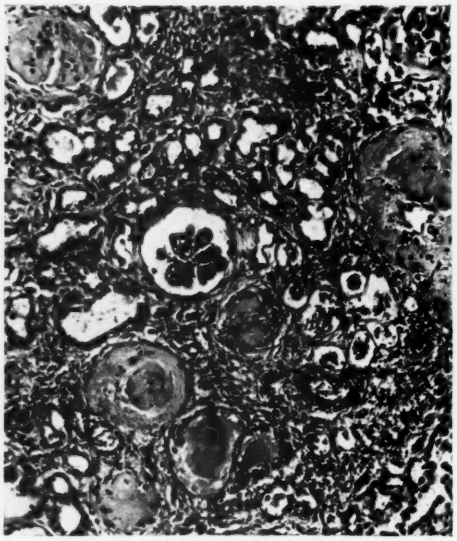

FIG. 8. Diabetic glomerulosclerosis. Late stage, numerous glomeruli completely hyalinized (haemalum and eosin, ×110)

FIG. 9. Renal hypoplasia. The renal substance is diminished in amount, but the surface is smooth. Natural size

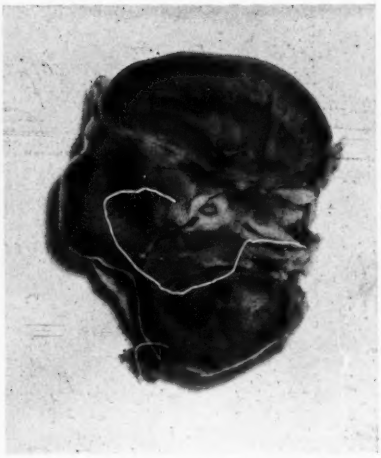

FIG. 10. Renal hypoplasia. A small kidney with but three medullary pyramids. Natural size

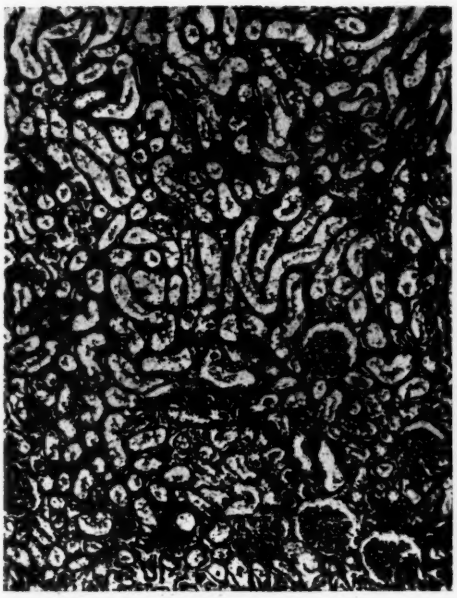

FIG. 11. 'Dehydration kidney.' There is generalized dilatation of cortical tubules which are lined by atrophic epithelium (haemalum and eosin, ×45)

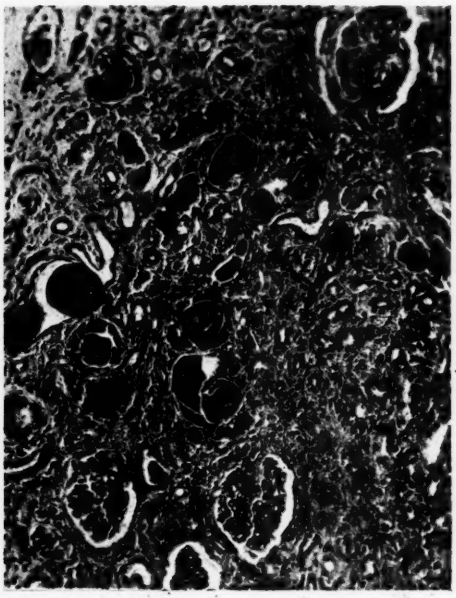

FIG. 12. Multiple myelomatosis. The cortical tubules contain numerous highly eosinophilic homogeneous casts (haemalum and eosin, ×70)

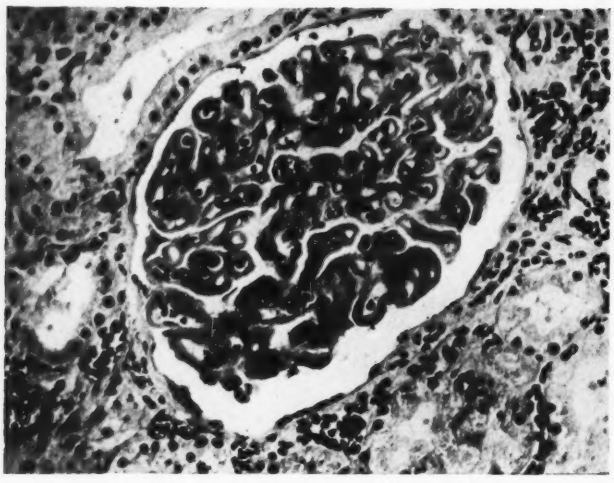

FIG. 13. Disseminated lupus erythematosus. Glomerulus showing the characteristic 'wire-loop' lesions (haelum and eosin, ×225)

FIG. 14. Pheochromocytoma and malignant nephrosclerosis. The kidney shows the characteristic cortical mottling and there is no contraction. The pheochromocytoma in the left adrenal is also shown. Reduced to 3/4ths natural size (Case 6)

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CONGENITAL TOXOPLASMOSIS[1]

By W. G. WYLLIE and H. J. W. FISHER

With a Note on the Pathology by I. A. B. CATHIE

(From The Hospital for Sick Children, Great Ormond Street, London)

With Plates 7 and 8

Historical Review

Human infection by the protozoon toxoplasma is best known and commonest in its infantile form of a disseminated encephalomyelitis, associated with cerebral calcification and bilateral focal (macular) retinochoroiditis. Many patients succumb soon after birth, and others survive beyond infancy with defective vision and mental deficiency. Based on a clinical, ophthalmological, and radiological examination, the diagnosis to-day can usually be made with confidence. Proof of the nature of the infection is provided by the clinical pathologist, either by transmitting the toxoplasma to animals, using cerebrospinal fluid from a suspected case *in vivo*, or an emulsion of necrotic cerebral tissue from autopsy material, or by detecting antibodies to the toxoplasma in the sera of the infant, its mother and siblings. Finally, in fatal cases, the morbid anatomist demonstrates the presence of toxoplasma in nervous and other tissues.

Historically it is of interest to note that recognition of the protozoon toxoplasma was due to the animal researches of Nicolle and Manceaux and of Splendore in 1909. There appears to be one species only, as cross-immunization can be produced experimentally with toxoplasmata from different sources. The toxoplasma has been found widely distributed in animals, birds, and reptiles in every continent. Human infection appears to depend upon association with infected animals, commonly dogs, cats, rabbits, or birds, or with rats and mice in infested dwellings, probably without an intermediate vector. Morphologically, the toxoplasma presents many variations in fresh and stained specimens (Plate 7, Fig. 1). It is commonly described as a crescentic organism, 2 to 4 microns wide, and 4 to 7 long, more pointed at one end than the other, and with a large central chromatin mass. Sabin (1942*a*) states that in development it becomes pyriform, oval, or round, and that numerical increase is by longitudinal fission. Another appearance is that of a cluster of organisms in a rounded pseudocyst, 8 to 20 microns in diameter. In stained sections, the toxoplasma is seen intra- as well as extracellularly. In human patients it has been found in central nervous tissue, retina, heart, skeletal muscles, lymph nodes, intestinal mucosa, omentum, kidney, pancreas, adrenals, ovaries, testes, and thyroid. In the congenital infantile cases a definite predilection exists for nervous tissues, including the retina, notably in the macular area.

[1] Received May 18, 1949.

Thirty years after the recognition of toxoplasma in animals, the first human case of the infantile type, with transmission of the disease to animals, was reported by Wolf, Cowen, and Paige (Case 2, 1939*a*, *b*). To these authors most of the credit is due for classifying the clinical and pathological features of the disease as it affects the infant. Reports of human toxoplasmosis at all ages have since been published in increasing numbers from North and South America, Czechoslovakia, Sweden, Norway, Holland, France, and Corsica. So far in Great Britain only one case, in an infant of four months, has been reported by Jacoby and Sagorin (1948). In this instance, proof of infection was supported by the finding by Dr. Sven Gard of Stockholm of neutralizing antibodies, weakly positive in the serum of the infant, and strongly positive in that of the mother. The case we have to describe is that of a girl of five years, apparently infected congenitally *in utero*. A record is appended of the serological methods employed in proof of the infection in mother and child.

A survey of the years between 1909 and 1939 leaves no doubt that instances of human toxoplasmosis, even in its florid infantile form, must often have passed unrecognized. The paediatricians included them under such titles as acquired hydrocephalus, encephalomyelitis neonatorum, and birth trauma. Ophthalmology provides a rich field in which to correlate the specialized retino-choroidal signs with the clinical and radiological features. Retrospective studies convinced Wolf, Cowen, and Paige (1939*b*) that the two cases from the Babies Hospital, New York, of infants dying within a month after birth with signs of encephalomyelitis and focal retinochoroiditis (reported No. 1 in 1937, No. 2 in 1939), were instances of human toxoplasmosis. They further upheld the view, already expressed by Levaditi (1928), that the case reported by Janku (1923, Czechoslovakia) of an infant living to 11 months with hydrocephalus, microphthalmos, and 'coloboma' of the macula lutea, and that reported by Torres (1927, Brazil) of an infant dying at two days of age, were both instances of toxoplasmosis. In addition, Wolf, Cowen, and Paige recognized the disease in Richter's case (1936) of an infant seven weeks old. In these five patients the toxoplasma was found *post mortem*. In 1942, in describing three additional congenital infantile cases, they also demonstrated toxoplasmosis in sections of the brain in Cornelia de Lange's case (1929) of 'chronic acquired hydrocephalus'. Besides these proven examples, Wolf and Cowen had in 1938 pointed to the clinical resemblance between their own early cases and those in infants described by Wohlwill (1921), Brandt (1934), and Fischl (1897 and 1899). Similarly, Pinkerton and Weiman (1940) proved a case reported by Hertig (1934) to be one of toxoplasmosis. Callahan, Russell, and Smith (1946), in reporting on a female infant three days old, in whom toxoplasma was found at autopsy, said that in a retrospective study of 10,000 autopsies at the St. Louis Children's Hospital, they proved the diagnosis in five other infants who had died from three hours to two months after delivery.

Binkhorst (1948*b*), in a comprehensive monograph on toxoplasmosis, emphasized the ophthalmological findings, and mentioned 20 cases of proved or presumable toxoplasmic retinopathy and retino-encephalopathy. In two infants,

of whom one, a premature child, died eight weeks after birth, the other at three months of age, toxoplasmata were found in the cerebrospinal fluid. Of the remainder, Cases 3 to 13, aged from 14 months to 54 years, all had retino-encephalopathy and a positive serum-neutralization test for toxoplasmosis. Cases 14 to 20, aged from one to 20 years, showed retino-encephalopathy resembling that due to toxoplasmosis, but of undetermined origin. In another ophthalmological study Johnson (1946) states that of 32 selected patients with retinochoroiditis tested serologically, 20 showed toxoplasma-neutralizing antibodies.

Clinical and Pathological Picture

The clinical signs are classified according to age-groups. The largest group, with the most constant features, is that of the congenital infantile type. Many of these patients die in earliest infancy, while others live on with visual and mental defects. Sabin (1941) described the acquired type in older children, taking the form of an acute encephalitis, which may be fatal, or may end in recovery without sequelae. Tomlinson (1945) reported finding toxoplasma *post mortem* in the heart-muscle and lungs of a negress of ten years and eight months, who had symptoms of malaise, fever, and jaundice, and a blood picture of sickle-celled anaemia. There were no neurological or ocular symptoms. Castellani (1914) claimed to have found toxoplasma-like organisms in the spleen of a boy of 14 years in Ceylon, in whom the symptoms before death were fever, anaemia, and splenomegaly. In young adults an acute illness resembling the typhus–spotted-fever group of diseases, with predominant pulmonary signs, has been described (Pinkerton and Henderson, 1941). Toxoplasmic infection has been discovered up to any age, even without any clinical indication of its presence. In a Jewish tailor, who had pyrexia 103·4° F., macules on the trunk, anorexia, diarrhoea, muscular pains, and colic, and subsequently recovered, Sylverton and Slavin (1946) found toxoplasma by biopsy in a piece of gastrocnemius, and successfully transmitted it to animals.

Obviously, there must also be a subclinical type of infection leaving neutralizing antibodies, but capable in the pregnant woman of transmitting toxoplasma to the foetus. The foetus is especially susceptible to infection, which attacks mainly the central nervous system and retinae.

Symptoms in the infantile form. Symptoms of cerebral disturbance are apparent at birth or soon afterwards, and seldom with a latent period longer than six weeks. Most of those who survive have had ocular and cerebral disturbances from birth. Muscular twitchings and convulsions occur in most cases. Jaundice, cyanosis, irregular breathing, and drowsiness are common, and the temperature may be raised, subnormal, or erratic. Enlargement of the skull at or soon after birth occurs in the majority of fatal cases, but heads of normal size, and microcephaly, are also seen. Commonly there are visible abnormalities of the eyes, microphthalmos and enophthalmos. Associated ocular disturbances are nystagmus, or rolling movements of the eyes, strabismus, unequal pupils, and downward turning of the eyes; less commonly, iridocyclitis and cataract.

Disturbances of the central nervous system are soon apparent; crossed-leg spasticity, hemiplegia, rotation of the head to one side, facial nerve palsy, and opisthotonus have been described.

In proof of the intra-uterine foetal infection, and the possibility of the disease passing from the acute to the chronic stage *in utero*, we may instance Case 4 of Paige, Cowen, and Wolf (1942), in which the enlarged head of the toxoplasmic infant required craniotomy at delivery. Kean and Grocott (1948) reported the case of an infant three months premature, who died 10½ hours after delivery. On opening the skull, the brain was found to be a collapsed, gelatinous, almost shapeless mass. Intense granulomatous retinochoroiditis was present in both eyes, and toxoplasmata from an emulsion of the brain tissue were passed by inoculation through several series of guinea-pigs. Zuelzer (1944) reported three cases, of which two were identical twins, one with intense hydrocephalus dying one month after delivery, the other with mild hydrocephalus being alive at seven months. Bamatter (1947), in Switzerland, reported premature twins, one of whom, a female, had convulsions, nystagmus, and retinochoroiditis, and died on the twenty-seventh day of life; the other, a male, was probably affected, and died on the thirtieth day from ulcerative enterocolitis. The mother, in the latter months of pregnancy, had as an inseparable companion her favourite cat. She presented cutaneous petechial lesions. Prematurity is common, and in many of the anamneses the mother's health during pregnancy is said to have been poor. Few studies of the placenta have been made, but in Kean and Grocott's case it was stated to be abnormal in appearance and colour. Still-births have followed the birth of an affected infant, but so have normal children. Callahan, Russell, and Smith (1946) reported that a female infant with toxoplasmosis died three hours after delivery, but 15 months later the mother gave birth to a normal child. Neuhauser and Tucker (1948) have described three cases in newly born babies of a fatal meningo-encephalitis, closely resembling that due to toxoplasmosis, with hydrocephalus and cerebral calcification, and due to infection by the fungus *Torula histolytica*.

Callahan, Russell, and Smith tabulated symptoms other than those of the central nervous system, in 18 infantile cases, as follows: splenomegaly, 7; hepatomegaly, 9; jaundice, 5; purpuric spots, 3; fever, 9; subnormal temperature, 7; pulmonary signs, 11; upper respiratory infection, 9; vomiting, 6; diarrhoea, 4; feeding difficulties, 9.

Clinical signs in the infantile form. The four cardinal signs of infantile toxoplasmosis are (1) meningo-encephalo-myelitis, with or without enlargement of the skull, (2) ocular signs, especially bilateral retinochoroiditis, which is usually macular and occasionally peripheral as well, (3) radiological evidence of cerebral calcification, and (4) great enlargement of the lateral ventricles, most marked in their parietal, temporal, and occipital portions, as shown by ventriculography.

(1) The encephalo-myelitic signs, in infants who die early, have already been mentioned. As to those who survive infancy, Koch, Wolf, Cowen, and Paige (1943), in six children of two to eleven years old, found speech defect, mental retardation, and ocular defects, notably retinochoroiditis. In five of these six

cases cerebral calcification is recorded. (2) The typical macular retinochoroiditis must frequently have been in existence before birth, and in its chronic state leaves large white areas of retinochoroidal atrophy, with pigment deposition. In one of Binkhorst's patients, a girl of six years, the right eye showed chronic macular retinochoroiditis; in the left eye there was some pigment-displacement of a brownish colour at the macula, first observed in her fifth year, and surrounded by several small active retinal lesions, which became completely reabsorbed within a few months. Cerebrospinal fluid obtained from this patient by lumbar puncture, centrifugalized and inoculated into mice and guinea-pigs, produced toxoplasmosis. In a child of three days, Wolf, Cowen, and Paige (1939*b*) reported an early change consisting of irregular reddish-brown areas in each macular region. Optic atrophy is frequently found in association with the focal retinitis. Johnson (1946) recorded the case of a mother, aged 22 years, whose retinochoroiditis flared up in three successive pregnancies; Binkhorst (1948*b*), that of a woman of 30 years, who became ill and developed bilateral acute retinochoroiditis, and a year later gave birth to a daughter who had retinochoroiditis in both eyes. Retinal involvement is rare in the acquired toxoplasmosis of older children and adults. It was not present in Sabin's (1941) two patients of six and eight years of age, with acquired toxoplasmosis and encephalitis. (3) Cerebral calcification occurs in multiple linear specks, 2 to 5 mm. long, in most infantile cases, but it is not an essential sign. At post-mortem, nodules of calcification are found, especially in the parietal and occipital cerebral cortex, basal ganglia, caudate nucleus, and thalamus. It is rarely observed in adults. Johnson stated that it was not found in patients whose age, when symptoms of toxoplasmosis began, was known to have been over 15 years. Cerebral calcification can occur in the foetus *in utero*, having been demonstrated radiologically shortly after birth. Mothers of toxoplasmic infants have in a few instances been found to have cerebral calcification (Crothers, 1943; Johnson, 1946). Johnson reviewed, from the literature and from his own records, 45 cases of congenital toxoplasmosis with retinochoroiditis and a positive antibody-neutralization test, and found only seven in which cerebral calcification was absent. Dyke, Wolf, Cowen, Paige, and Caffey (1942) found calcification in eight out of nine cases examined radiologically. (4) Internal hydrocephalus. Some confusion arises here because, although the majority of infant sufferers have abnormal expansion of the skull—hydrocephalus—others have microcephaly, or normal-sized heads. But by ventriculography, all show degrees, often extreme, of ventricular enlargement. The enlargement of the lateral ventricles is most noticeable in the temporal, parietal, and occipital areas, and is produced in two ways. There may be a granuloma-tissue blockage of the foramina of Munro, or of the iter of Sylvius; or else the formidable degree of disseminated necrosis, especially in relation to the ventricular walls, may cause shrinkage of the hemispheres, with a replacement 'internal hydrocephalus' as a natural sequel. Dyke, Wolf, Cowen, Paige, and Caffey, referring to their radiograph of a hydrocephalic infant aged two weeks, drew attention to the relatively moderate destruction of the frontal lobes compared to other

parts of the hemispheres. This appearance by ventriculography was strikingly obvious in our own patient, in whom, however, intelligence was remarkably good. Some authors have remarked on a honeycomb appearance produced by air in the enlarged ventricles, and have suggested that the raised viscosity of the cerebrospinal fluid leads to bubbles of air being seen in ventriculograms. Another possible cause of this appearance is the irregular contour of the necrotic walls of the ventricles, which may be in communication with surrounding cysts in the hemispheres. The cerebrospinal fluid in most infantile cases is xanthochromic, with a pleocytosis, lymphocytic in type, reaching 100 or 200 per c.mm., and with a total protein up to more than 500 mg. per 100 c.c.

Toxoplasmosis in older children. Beyond infancy, Sabin (1941) described two cases of acquired toxoplasmosis, in children six and eight years old. In the former, the illness commenced with severe headache, followed by convulsions, vomiting, and an unsteady gait, and death occurred on the tenth day. The cerebrospinal fluid showed a monocytic pleocytosis of 2,200 per c.mm. The second patient had signs of encephalitis for 10 days, and made an uneventful recovery. The spinal fluid contained 200 cells per c.mm., chiefly lymphocytes, and when inoculated into guinea-pigs, produced toxoplasmosis. Our own patient is almost certainly one who has survived intra-uterine infection, as did the six children described by Koch, Wolf, Cowen, and Paige (1943).

Necropsy Findings

A disseminated encephalomyelitis is constantly found, showing to the naked eye depressed yellowish areas of necrotic softening of the cortex, with a contiguous leptomeningitis. Lesions are present in the cortex and in the white matter, especially adjoining the ventricles, and vary from miliary granulomata to areas of necrosis and caseation, or cavity formation. The basal ganglia are heavily involved, and the enlarged ventricles are lined with a soft, often greyish-yellow, granulomatous tissue. The spinal cord also loses its architectural markings, and shows areas of softening and necrosis. The capillaries show endothelial hyperplasia, and the small vessels adventitial inflammation (Wolf and Cowen, 1937). Toxoplasmata are found intra- and extracellularly, but pseudocysts have not been seen in relation to the disseminated granulomata. In infants, the central nervous system and retina are the chief habitat of the organisms, but they may be found in many other organs, as in adults. In the eye, toxoplasmata, single and in pseudocysts, are plentiful in the edges of the focal necrotic retinitis. In the early stages of ocular inflammation, Binkhorst (1948*a*, *b*) found retinitis occurring first, with relatively little damage to the choroid, except by oedema and cellular infiltration.

Case Report

The patient, an illegitimate child, was a girl aged five years, first seen by us on February 2, 1949. Her birth was normal, at full term, and weight at birth 6 lb. 12 oz.; her mother's health was good during pregnancy. The mother always thought the child's sight was abnormal from birth, as rolling movements of her eyes were noticeable from the first month. When learning to walk, she

often bumped into things, and a squint was noticed at the age of three months. After this her vision did not deteriorate; she habitually made groping movements at objects in her vicinity. She developed normally, mentally and physically, and had no illnesses. Her head was always a peculiar shape, narrow anteriorly and broader posteriorly; on examination, its circumference was 21½ inches. Her father had good health, and was killed in the war. Her mother was healthy; two years before the child was born she lived for a year on a farm, where she had an illness, probably rubella, with a rash on her body, diarrhoea, and headache.

On December 23, 1948, the child felt queer, took two glasses of water, and lapsed into unconsciousness. One hour later, she was stiff and had clonic movements of her right side. Next day she felt well again. On February 4, 1949, she had another fit, at 11.30 a.m., and was incontinent of urine. She had never suffered from headache, and had always been very talkative and precocious in her speech.

On examination, her general condition was good, height 3 ft. 10 in., and weight 42 lb. Her speech and gait were normal, but there was bilateral pes cavus. The liver edge was palpable, but the spleen was not felt. The vision of the left eye was nil; the right eye showed extreme myopia, and she could recognize letters half an inch big only at two inches distance. *Ophthalmological examination* was made under anaesthesia by Mr. J. H. Doggart, who reported: 'Extensive opacity in the lower half of the right lens, chiefly implicating the superficial layers anteriorly and posteriorly. Mobile vitreous opacities, chiefly in the lower region of each eye. *Fundi*: both eyes show huge irregular overlapping areas of choroido-retinal atrophy, together with some erratic pigment proliferation. The lesions involve the macular and juxta-papillary areas, and extend far into the periphery. Towards the periphery, some of the affected regions display diffuse cloudiness, indicating that some of the choroido-retinal inflammation is recent. These appearances support the diagnosis of toxoplasmosis' (Plate 8, Figs. 5, 6). She had a weakness of the left external rectus muscle, and coarse wandering nystagmus was always present. The pupils were circular and equal, and reacted to light and accommodation. Both eyes showed some degree of enophthalmos.

Skull X-ray (Plate 7, Fig. 2). Throughout the frontal and parietal lobes there are scattered areas of calcification of irregular size, with linear calcification above the pituitary fossa, which, in itself, is normal in size. The digital markings on the vault are perhaps excessive for the age of the patient, and there is suture diastasis. The mother's skull shows no radiographic abnormalities.

Ventriculography (Plate 7, Figs. 3 and 4). There was good filling of the ventricular system, showing extreme ventricular enlargement. The third ventricle and septum pellucidum stood erect in the midline. There was dilatation of the anterior horns of the lateral ventricles, and gross dilatation of the bodies, trigones, and occipital and temporal horns, indicating gross cerebral atrophy, only the frontal lobes being spared.

Electro-encephalography. This showed a grossly abnormal record, containing little which was recognizable as normal rhythmicity, and a wide range of high voltage slow waves, for the most part arrhythmic. A 3-cycle-per-second rhythm was an exception, and was more prominent on the right side. No definite epileptic activity occurred, nor was it possible to distinguish any definite focus. At this age, such great abnormality might be constitutional, but even so it is more likely to have an organic basis. This must either have been deep, perhaps in the right hemisphere, or generalized, such as a raised intracranial pressure, or a toxic state.

Mental state. The child was talkative and precocious, with a preference for

the male sex. She masturbated frequently. Her intelligence seemed good, and her behaviour abnormal, but the blindness made assessment difficult. Dr. M. Creak, Child Psychiatrist (Dept. of Psychological Medicine), reported the child to be above the average intelligence for her age, and that she used her hands intelligently.

Other tests. The Wassermann reaction was negative in mother and child. A blood count showed red cells 4,360,000 per c.mm., white cells 9,300 per c.mm., and neutrophils 64 per cent. The cerebrospinal fluid was clear, not under pressure, and contained 3 cells per c.mm., protein 30 mg., sugar 50 mg., and chlorides 720 mg. per 100 c.c.; the Nonne-Apelt test was negative.

Physical examination of the mother was negative. There was no retinochoroiditis.

Note on the Pathology

Neutralizing antibodies in human sera. In an antibody neutralizing test, Heidelman (1945) obtained a weakly to strongly positive result in 63 per cent. of a series of patients with congenital retinochoroiditis, and in six out of seven mothers of infants with congenital retinopathy. Sabin (1942*b*), in a group of 151 selected individuals, including a large number of children with nervous and ocular diseases and in many cases their mothers, found evidence of neutralizing antibodies in the sera of 59. Of 15 children presumably infected with toxoplasma *in utero*, he observed that 13 of the mothers gave a positive antibody neutralizing test. Similarly, Johnson and his fellow workers (1946), reviewing presumable cases of toxoplasmosis from the literature and from their own clinic, reported that of 45 patients with retinochoroiditis and a positive serum antibody test, only seven showed no radiological evidence of cerebral calcification. They further found that of 32 selected patients of various ages with central retinochoroiditis, active or inactive, 20 possessed neutralizing antibodies in their sera. Crothers (1943) recorded nine children, belonging to five families, in whom a clinical diagnosis of toxoplasmosis was supported by serological evidence. All the children had cerebral calcification, and seven of them had inactive retinochoroiditis. In two of the families the disease affected two children, and the mother of one of the pairs had cerebral calcification. Presence of antibody in the sera of healthy siblings is common. In a study of one family with a toxoplasmic member, Johnson found neutralizing antibodies in seven out of the total of nine children.

In normal people, and others with acquired retinochoroiditis, Heidelman found neutralizing antibody in the sera of 10 per cent.; Binkhorst (1948*a*, *b*), choosing 58 normal people at random, found antibody in the sera of six. Johnson stated that four laboratory workers dealing with toxoplasma research altered from negative to positive in their serum reactions, but no signs of illness occurred.

Laboratory diagnosis in the present case. So far no specific features have been reported in the clinical pathology of toxoplasmosis, and in the present case the cerebrospinal fluid was normal. The diagnostic methods available are isolation of the toxoplasma, the skin reaction to toxoplasmin, and the demonstration in the serum of neutralizing, complement-fixing, and cytoplasm-modifying antibodies.

Isolation of toxoplasma. No organisms were seen in centrifugalized deposits of the cerebrospinal fluid; mice inoculated with the fluid did not sicken, nor was any effect obtained when their organs were ground up and transmitted to further mice. In view of the burned-out stage of the disease in our patient, this result was not surprising.

Toxoplasmin test. Toxoplasmin prepared according to the method of Frenkel (1948) and Warren and Russ (1948) was inoculated intradermally, in a dilution of 1/10,000, into our patient and into three apparently normal children. No reaction was noted in the controls, but in our patient a zone of erythema developed within 24 hours and faded after 48 hours. This was interpreted as a doubtful result.

Neutralizing antibody. Tests for this antibody were performed by the rabbit-skin method of Sabin and Ruchman (1942), the patient's serum giving a doubtful result and her mother's serum a positive one. Prof. C. B. Beattie, of Sheffield University, kindly repeated this examination for us, and found the child to be positive and the mother doubtful. When mixtures of toxoplasma and serum were inoculated into the developing chick embryo, the sera of both mother and child reduced the number of lesions as compared with control sera.

Complement-fixing antibody. By the method of Warren and Russ (1948), the patient's serum showed a complement-fixing titre of 1/16, and her mother's a titre of 1/32. Warren (1948, personal communication) regarded a titre of 1/8 as doubtful, and 1/16 as positive.

Cytoplasm-modifying antibody. This antibody and a test for its presence have recently been described by Sabin and Feldman (1948). The patient's serum contained the antibody at a titre of 1/64, and her mother's serum at 1/128.

Conclusion. We did not expect to isolate the toxoplasma from this apparently healed patient, but the agreement, in both mother and child, between neutralizing, complement-fixing, and cytoplasm-modifying tests appears in itself to justify the diagnosis of toxoplasmosis.

Summary

1. The literature of congenital toxoplasmosis is reviewed.
2. The clinical, radiological, and pathological features are discussed.
3. An unusual case of the congenital variety is described.
4. A note is appended on the serological methods of diagnosis.

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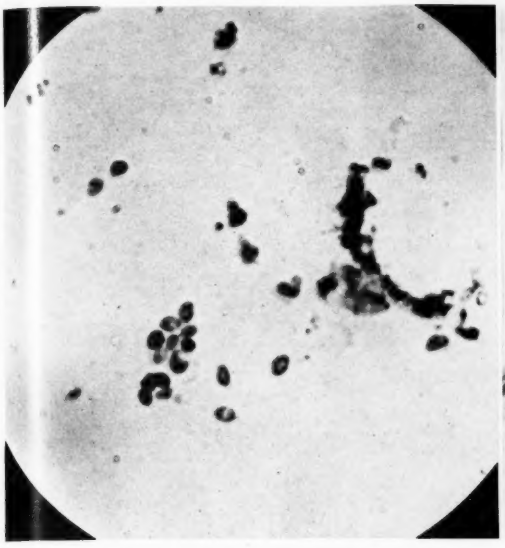

FIG. 1. Toxoplasmata from mouse peritoneal exudate, stained with methylene blue (×260)

FIG. 2. X-ray of the skull, showing diffuse calcification in the frontal and parietal lobes. There are increased digital markings on the vault

FIG. 3. Ventriculogram. Lateral view, showing gross dilatation of the lateral ventricles

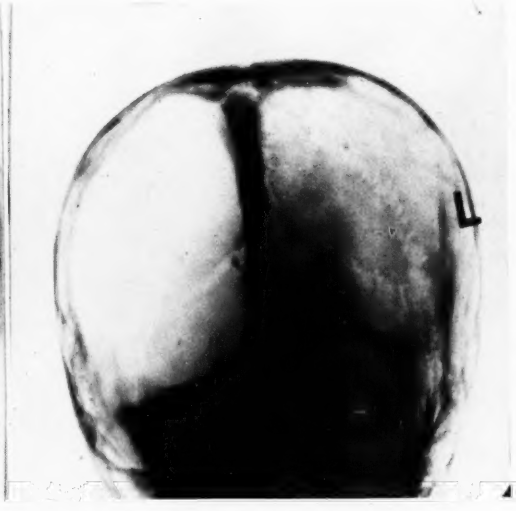

FIG. 4. Ventriculogram. Antero-posterior view

FIG. 5. *Right*

FIG. 6. *Left*

The ocular fundi, showing areas of retinochoroidal atrophy and pigmentation

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POSTMENOPAUSAL OSTEOPOROSIS, CLINICAL MANIFESTATIONS, AND THE TREATMENT WITH OESTROGENS[1]

By IAN A. ANDERSON

(From the Department of Clinical Chemistry, University of Aberdeen, and the Metabolic Ward, Aberdeen Royal Infirmary)

With Plates 9 and 10

Introduction

It has long been accepted that rarefaction of the bones is one of the atrophic processes that constitute the picture of senility. Recognition of a syndrome in which such rarefaction affected chiefly the spine and was often associated with pain in the back led to the description of this syndrome as senile osteoporosis or osteomalacia of the spine. Within the last 10 years several series of cases have been reported, including those of Meulengracht, 1939; Black, Ghormley, and Camp, 1941; Albright, Smith, and Richardson, 1941; Burrows and Graham, 1945. These investigations have brought out two important aetiological points —that the age incidence does not justify the appellation senile, and that women are far more frequently affected than men. The peak of incidence, according to the investigators mentioned above, is in the age-group 60 to 65 years, and out of a total number of 289 patients in the four series of cases, no fewer than 234 were women.

Clinical and Radiological Findings

The characteristic clinical and radiological findings, which have been completely described in the reports quoted above, need only be summarized here. The patient, usually a woman of about 60 years of age, first notices weakness and a dull ache in the lower part of the back. This may be aggravated, especially as the result of a slight jar or fall, to acute and often agonizing pain which may persist for weeks. As the condition progresses spinal deformity develops, usually a rounded kyphosis of the dorsal region, sometimes with reduction of the normal lordosis of the lumbar region or else a compensatory exaggeration of this feature. There is usually considerable limitation of spinal movements due to muscle spasm. Tenderness on pressure over the spinous processes is not severe, but jarring or bending the spine usually elicits pain. The most striking radiological change is a uniform rarefaction of the affected bones, chiefly the spine and pelvis; the long bones and especially the skull remain comparatively unaffected. In the lower dorsal and lumbar regions the vertebral bodies become

[1] Received June 17, 1949.

biconcave and the intervertebral disks biconvex and thickened, the so-called 'fish spine' appearance. One or more of the biconcave vertebrae may be narrowed anteriorly so that its body becomes wedge-shaped, while sometimes actual collapse of a vertebral body may be seen.

Aetiology

The comparatively early age of onset, the marked preponderance in women, and the fact that only a minority of elderly persons develop the clinical and radiological manifestations described above, have led observers to the conclusion that spinal osteoporosis is to be regarded as a disease entity rather than as merely one of the atrophic processes that characterize senility. Considerable speculation has arisen as to the aetiology of the syndrome, and the following hypotheses have been advanced to explain its development: dietary deficiency, achlorhydria, and endocrine imbalance.

Dietary deficiency. In view of the well-established causal relationship between an inadequate intake of calcium and vitamin D and the characteristic skeletal rarefaction seen in osteomalacia, it is not surprising that a dietary deficiency of calcium and vitamin D (Meulengracht, 1939) or of phosphorus (Burrows and Graham, 1945) has been suggested as an explanation of the development of spinal osteoporosis. Other observers (Black, Ghormley, and Camp, 1941; Albright, Smith, and Richardson, 1941) have been equally emphatic that dietary deficiency plays no part in the causation.

Achlorhydria. Because of finding achlorhydria in eight out of 19 cases of spinal osteoporosis, Meulengracht (1939) concluded that this was probably a causal factor in the relevant cases, through an interference with the utilization of dietary calcium. But as Schmidt and Greenberg (1935) pointed out in their review, animal experiments have shown that alkalinization of the diet to the extent of neutralizing or even making alkaline the gastric juice does not interfere with the retention of calcium, but leads only to an increase in faecal calcium at the expense of urinary calcium.

Endocrine imbalance. Endocrine glands other than the parathyroids influence the state of calcification of the skeleton; for example, osteoporosis is often present in long-standing cases of thyrotoxicosis, and osteoporosis chiefly affecting the spine is a characteristic feature of Cushing's syndrome. In a series of papers, Albright and his colleagues (Albright, Bloomberg, and Smith, 1940; Albright, Smith, and Richardson, 1941; Reifenstein and Albright, 1947; and Albright, 1947) have adduced convincing evidence that the spinal osteoporosis of elderly women is also the result of an endocrine imbalance. There is a considerable body of experimental evidence that oestrogens influence bone formation. In female birds there is a marked rise in the serum-calcium level and hyperossification in the marrow cavities of the bones before ovulation, with reversion to normal after ovulation (Kyes and Potter, 1934). Pfeiffer and Gardner (1938) showed that these effects were due to oestrogens by inducing similar changes in both male and female pigeons by the injection of oestrogens. The observations were extended to mammals with less striking results. No

consistent changes occur in the serum-calcium level after the injection of oestrogens, but in mice and young rats hyperossification of the skeleton follows prolonged treatment.

Impressed by the relative frequency of spinal osteoporosis in women who had suffered either a natural or artificial menopause and by the experimental demonstration of the effects of oestrogens on bone formation mentioned above, Albright, Bloomberg, and Smith (1940) investigated the effect of oestradiol benzoate on the calcium and phosphorus metabolism in three women suffering from what these authors have termed postmenopausal osteoporosis. They demonstrated that this oestrogen promoted a considerable retention of calcium and phosphorus through a reduction of both the faecal and urinary excretion. Oestrogen therapy also lessened or eliminated the pain in the bones and produced an improvement in the general well-being. Radiological evidence of increased bone formation was naturally difficult to obtain, but the results in the longest-treated cases were claimed to be fairly convincing. From these and other investigations Albright (1947) has concluded that bone formation is influenced by certain of the steroidal hormones. According to his hypothesis the steroidal hormones promoting anabolism of protein (testosterone, the androgenic hormone of the adrenal cortex, and oestrogens) stimulate the osteoblasts, while one group of hormones, the 'sugar-active' corticoids of the adrenal cortex, which inhibit protein anabolism, depresses the activity of the osteoblasts. In the normal adult, male or female, the opposing effects of these hormones are in balance. At the menopause the sudden withdrawal of oestrogen tends to tip the balance in favour of inhibition of osteoblastic activity, so that the laying down of organic matrix fails to keep pace with bone resorption, and a reduction in bone substance, so-called postmenopausal osteoporosis, results. Decreased production of the androgenic hormone of the adrenal cortex and, in the male, of testosterone at a later age, somewhere about 70 to 80 years, in the presence of continued production of 'sugar-active' corticoids at a normal level is considered by Albright to be the cause of senile osteoporosis. According to this theory, osteoporosis, whether postmenopausal or senile, is not a disorder primarily of calcium or phosphorus metabolism, but one of tissue metabolism. To explain by this theory why only a proportion of women develop clinical evidence of osteoporosis some years after the menopause, one would have to assume that in such patients the endocrine imbalance is excessive as compared with women who do not develop the syndrome, possibly because the production of 'sugar-active' corticoids is set at a higher level or because of a smaller extragonadal (adrenocortical) production of oestrogen.

The metabolic study described in the present paper was commenced when Albright and his colleagues had published only the results of their investigations on the effect of natural oestrogens, and was directed towards answering the question of whether the synthetic oestrogen dienoestrol would have an action similar to that of the natural hormone in postmenopausal osteoporosis. During the course of this work Reifenstein and Albright (1947) reported one case of postmenopausal osteoporosis in which diethylstilboestrol promoted calcium

retention. Since the results obtained in the experiments described below differed in certain respects from those of Albright and his colleagues, the investigation was continued in an effort to determine the optimal levels of calcium and phosphorus intake for the action of dienoestrol on the skeleton. Calcium, phosphorus, and nitrogen balances were carried out at different levels of intake of calcium and phosphorus in five cases of postmenopausal osteoporosis before and during the administration of dienoestrol. In one case the effect of giving testosterone propionate in addition to dienoestrol was investigated. Clinical data relating to the patients are given in the Appendix.

Methods

At each level of calcium and phosphorus intake a constant weighed diet was given. Distilled water was used in cooking and drinking. Urine and faeces were collected in three-day periods, the faeces being separated into these periods by the administration of two capsules each containing 0·3 gm. of carmine at the beginning of each period. To ensure accuracy in estimating the intake, a 25 per cent. aliquot portion of every item of food given to the patient was set aside each day and collected in three-day periods for analysis, from which the total intake could be calculated. Food rejected by the patient or vomitus was analysed and the results subtracted from the total intake. Food, urine, and faeces were analysed for calcium, phosphorus, and nitrogen by the methods given below.

Blood. Throughout the experiment fasting samples of blood were collected usually at the beginning of every fourth period. Calcium (Clark and Collip, 1925), inorganic phosphorus (Youngburg and Youngburg, 1930), and alkaline phosphatase activity (King and Armstrong, 1934) were estimated in the serum, and the carbon dioxide combining power of the plasma was determined by the volumetric method of Van Slyke and Cullen (1917).

Urine. Calcium was estimated by a modification of the method described for the analysis of calcium in foodstuffs in Technical Communication No. 9 of the Imperial Bureau of Animal Nutrition (1937). Total phosphorus was estimated by digesting 2 c.c. of urine with 2 c.c. of 60 per cent. perchloric acid on a sand-bath, and applying a modification of the Youngburg and Youngburg (1930) method for serum inorganic phosphorus to an aliquot portion of the diluted digest. Total nitrogen was determined on a 2 c.c. sample by a micro-Kjeldahl procedure utilizing the steam distillation technique described by Markham (1942). The accuracy of the urine collections was checked by determination of creatinine by the method of Folin as modified for photometric analysis (Hawk, Oser, and Summerson, 1947).

Faeces and diet. Faeces and minced diet samples were dried at 80° to 90° C. and the dry residues weighed and powdered. Aliquot portions for estimation of calcium were ashed in an electric furnace at 450° C. and analysed by the same method as for urine. Total phosphorus was estimated by further dilution of the ash extract and application of the modified Youngburg and Youngburg (1930) method for serum inorganic phosphorus. Total nitrogen was estimated by the Kjeldahl method, using the catalyst described by Chibnall, Rees, and Williams (1943) and applying the micro steam distillation technique of Markham (1942) to an aliquot portion of the diluted digest.

The chemical data are set out in Figs. 1 to 5. These have been constructed in accordance with the suggestions of Reifenstein, Albright, and Wells (1945) for a standardized mode of presentation of metabolic data in chart form. In each of the charts a broken line represents the theoretical phosphorus balance. According to Shohl (1939), over 90 per cent. of the body phosphorus is contained either in bone (with a calcium/phosphorus ratio of 2·23/1) or in protoplasm (with a nitrogen/phosphorus ratio in muscle of 14·7/1). Reifenstein, Albright, and Wells (1945) contended, therefore, that the sum of the phosphorus balances obtained by application of these ratios to the calcium and nitrogen balances—the so-called 'theoretical phosphorus balance'—should correspond closely with the actual phosphorus balance found by direct analysis, unless alterations occur in the amount of phosphorus compounds other than those of bone and protoplasm.

Results

Before investigation of the effect of dienoestrol on the calcium balance, each patient was studied during the administration of the low calcium diet recommended by Bauer, Albright, and Aub (1929) as a diagnostic procedure in disorders of calcium metabolism. Balance studies were preceded by a period of six days on this diet in order to secure equilibrium at the low level of intake. It has been found in this hospital that on a diet not adjusted to neutral ash content and containing about 0·43 gm. of calcium per three-day metabolic period, normal persons excrete 0·35 gm. to 0·40 gm. of calcium in the faeces and 0·35 gm. to 0·42 gm. in the urine, and have a negative calcium balance of 0·27 gm. to 0·40 gm. per period. On the low phosphorus content of this diet, 0·95 gm. to 1·30 gm. per three-day period, the faecal excretion is 0·29 gm. to 0·44 gm., the urinary excretion 0·92 gm. to 1·15 gm., and the negative balance 0·27 gm. to 0·30 gm. of phosphorus per three-day period.

Case 1. A single woman aged 48 years. Menopause at 42 years. There had been symptoms for two years before commencement of the experiment. The metabolic data of this patient are given in Fig. 1.

Part I. On the diagnostic low calcium diet the patient had an abnormally large negative calcium balance, averaging 0·76 gm. per three-day period and due entirely to an excessive excretion of calcium in the urine. The phosphorus excretion was about the same as that found in normal persons, but owing to the higher intake, the balance was positive. Albright, Smith, and Richardson (1941) suggested on theoretical grounds that an increased excretion of calcium and phosphorus in the urine might be expected in the early, but not in the late, stages of osteoporosis, and Albright, Burnett, Cope, and Parson (1941) demonstrated a very considerable hypercalcuria in an early case of disuse osteoporosis. It was therefore considered that the hypercalcuria found in the present case did not invalidate the clinical diagnosis of postmenopausal osteoporosis.

Part II. The patient was then placed on a calcium intake of 1·7 gm. daily (about twice the accepted optimal figure of 0·8 gm. daily), which was secured by giving a high calcium diet plus 6·25 gm. of calcium lactate daily, made up in 5 per cent. solution with water, and analysed directly for its calcium content. After six days to ensure equilibrium, balance studies were conducted for four three-day periods. Even on the high calcium intake, the patient was in marked negative calcium balance, the average loss of 0·704 gm. per period being almost

as great as on the diagnostic low calcium diet. In spite of the increase in phosphorus intake as compared with Part I, the phosphorus balance was negative, with an average loss of 0·112 gm. per period. This deterioration in the phosphorus balance is probably due to the high calcium intake relative to that of phosphorus, since Albright and Sulkowitch (1938) have shown that an increase

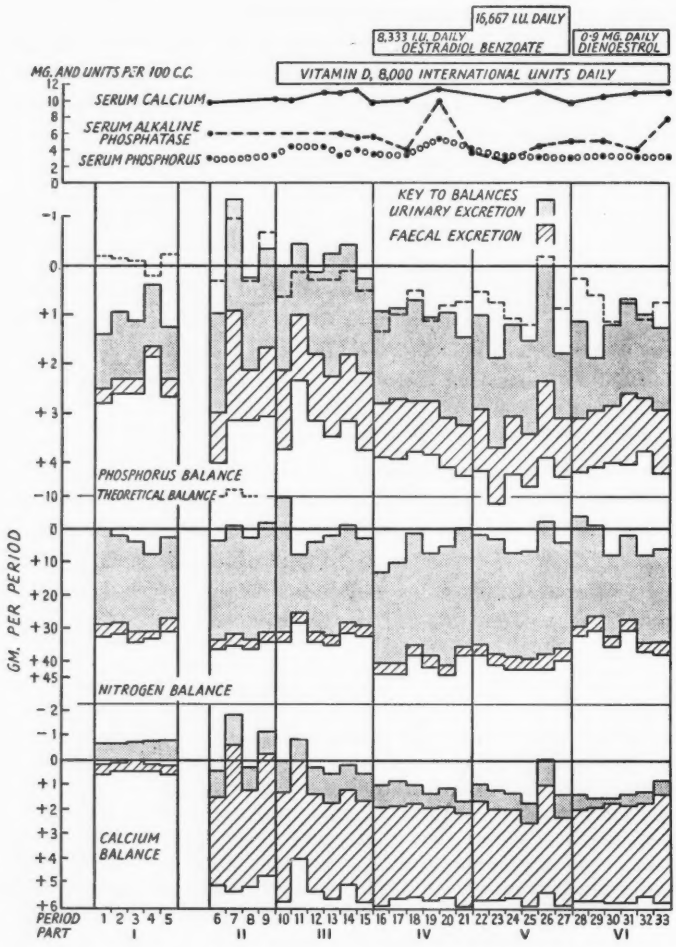

FIG. 1. (See note on p. 92.)

in the calcium intake reduces the retention of phosphorus by increasing its excretion in the faeces.

Part III. The patient had been treated in another clinic for a year and had been advised to take 3 gm. of calcium lactate and 2,000 i.u. of vitamin D daily. Although this dose of vitamin D should have been adequate as a prophylactic to compensate for lack of exposure to ultraviolet radiation through confinement indoors, it was decided to investigate whether a larger dose of vitamin D would have any effect on the calcium balance. Accordingly, 8,000 i.u. of vitamin D

per diem were given, along with the same régime as in Part II. A significant change in the calcium balance developed over the next six periods. On an intake of calcium that was approximately 0·2 gm. per period higher than in Part II, there was calcium equilibrium, which involved an increase in the retention of calcium of almost 0·8 gm. per period. There was no decrease in the urinary calcium excretion, and the enhanced calcium retention was due to a decreased faecal excretion, such as occurs in rickets under treatment with vitamin D. The patient had been in the Metabolic Ward for about a month without vitamin D being given; nevertheless, it is surprising that a minor degree of hypovitaminosis D could be induced in such a short time. The phosphorus balance was not affected by the administration of vitamin D and was still negative, with an average loss of 0·104 gm. per period.

Part IV. To determine whether the patient would show a metabolic response to oestrogen therapy, 5 mg. of oestradiol benzoate were injected intramuscularly every sixth day (equivalent to 0·83 mg. per diem) while the patient was on the same régime as in Part III, including vitamin D. Over the six periods of Part IV, the average calcium intake was unfortunately almost 0·5 gm. higher per period than in Part III, but the calcium balance became positive by over twice this amount. There was a well-marked reduction in the urinary calcium excretion, and the faecal excretion also fell, in spite of the fact that the calcium intake was larger. The phosphorus intake was almost 0·7 gm. greater per period than in Part III and the balance became positive, due to an increase in retention of almost 1·1 gm. per period. The nitrogen balance was more positive, but the nitrogen intake was about 9 gm. greater per period than in Part III. From the results in Part IV and those obtained in the later studies, it seems likely that the increased nitrogen retention was related to the larger intake rather than to the administration of oestrogen.

Part V. The dose of oestradiol benzoate was increased to 5 mg. every third day (equivalent to 1·67 mg. per diem), but the extent of the positive calcium balance remained almost exactly the same as in Part IV. An increase of 0·25 gm. per period in the positive phosphorus balance was probably due largely to an increase in the intake of 0·4 gm. per period.

Part VI. For six periods, oestradiol benzoate was withdrawn and 0·9 mg. of dienoestrol per diem given orally instead. There was a slight increase in the positive calcium balance, due to a further fall in the urinary calcium excretion. The extent of the positive phosphorus balance remained the same as in Part V. The serum calcium, inorganic phosphorus, and alkaline phosphatase were all within normal limits at the start of the experiment and showed no significant changes throughout.

There was a rapid onset of alkalosis when calcium lactate administration was begun in Part II, the alkali reserve increasing in 12 days from 64 to 103 volumes per 100 c.c. A similar but less dramatic development of alkalosis was seen by Anderson and Lyall (1939) in a patient with hypoparathyroidism complicated by chronic nephritis, who was, however, receiving twice as much calcium lactate as was given in the present instance. Renal function in the present patient was normal as judged by the urea clearance and concentration tests, and this failure of the kidneys to compensate for ingestion of an alkalinizing salt is inexplicable. To avoid the disturbance in the paths of excretion of calcium that alkalosis produces (Schmidt and Greenberg, 1935) sufficient dilute hydrochloric acid was added to the calcium lactate to restore the alkali reserve to normal and

keep it within normal limits. The actual phosphorus balance was more positive than the theoretical balance, except in Part III, where it was slightly negative, while the theoretical balance was slightly positive. Comparison of the actual weight curve with the theoretical weight curve (that is, the change in weight that would have occurred if the only alterations in weight had been due to gain or loss of protoplasm, as calculated from the scheme given by Reifenstein, Albright, and Wells, 1945), indicates (see Fig. 6) that the actual gain in weight was less than the theoretical gain, which suggests that some loss of extracellular fluid had occurred during the course of the experiment. Retention of phosphorus in extracellular fluid cannot therefore be invoked as an explanation of why the actual phosphorus balance was on the whole more positive than the theoretical balance.

Conclusions from Experiment 1

1. Administration of oestradiol benzoate in a dose of 0·83 mg. daily brought about retention of calcium in a patient who was in calcium equilibrium on a high calcium diet with added vitamin D. It might be argued that the reduction in faecal calcium excretion from Part III to Part IV betokened a further intensification of the vitamin D effect obtained in Part III, but the marked reduction in urinary calcium excretion suggests an increased utilization of absorbed calcium under the influence of oestradiol benzoate.

2. The effect of oestradiol benzoate on the calcium balance was not enhanced by doubling the dose to 1·67 mg. per diem.

3. The synthetic oestrogen dienoestrol, 0·9 mg. daily by mouth, an amount that was considered approximately equivalent in oestrogenic effect to 0·83 mg. of oestradiol benzoate, appeared to have at least as great an effect in promoting calcium retention as had the natural oestrogen. Reifenstein and Albright (1947) found that the maximum effect of oestradiol benzoate on calcium retention was not reached until after about 30 days of therapy and that the effect persisted for about 15 days after therapy was stopped. It might therefore be argued that the maintenance of a strongly positive calcium balance in Part VI was due not to any effect of dienoestrol, but merely to a persistence of the action of the oestradiol benzoate given in the previous periods.

4. Oestrogen therapy appeared to increase phosphorus retention also, although the results are less conclusive owing to variations in the level of phosphorus intake.

5. No significant or consistent changes in nitrogen balance accompanied the administration of oestrogen.

Case 2. A single woman aged 65 years. Menopause at 50 years. There had been symptoms for 13 years before commencement of the experiment. The metabolic data of this patient are shown in Fig. 2. The experiment was designed to demonstrate whether dienoestrol alone would promote calcium retention, and consisted of five parts, each comprising six three-day periods.

Part I. On the low calcium diagnostic diet, the patient's negative calcium and phosphorus balances were approximately the same as those found in normal persons, as would be expected, according to Albright, Smith, and Richardson

(1941), in the later stages of postmenopausal osteoporosis, when the skeleton has become reduced in substance.

Part II. The patient was then placed on the high calcium diet plus 6·25 gm. of calcium lactate daily that was given to Case 1, and after six days to ensure equilibrium, the metabolic study was resumed. The patient was just in positive

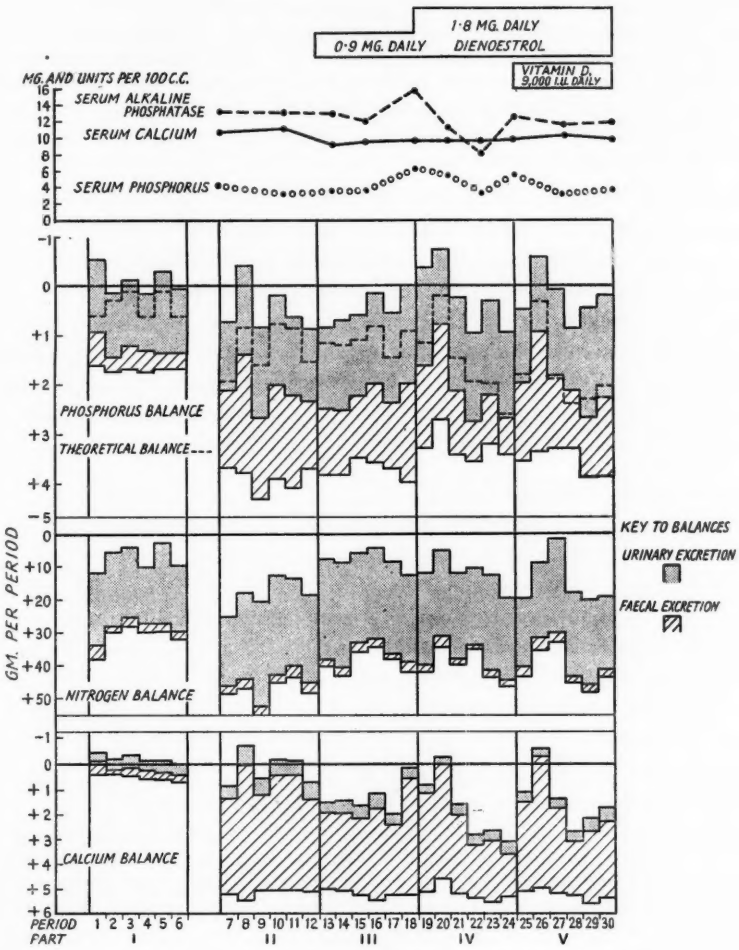
1·8 MG. DAILY
0·9 MG. DAILY DIENOESTROL
VITAMIN D 9,000 I.U. DAILY
MG. AND UNITS PER 100 C.C.
SERUM ALKALINE PHOSPHATASE
SERUM CALCIUM
SERUM PHOSPHORUS
PHOSPHORUS BALANCE
THEORETICAL BALANCE
GM. PER PERIOD
NITROGEN BALANCE
CALCIUM BALANCE
KEY TO BALANCES
URINARY EXCRETION
FAECAL EXCRETION
PERIOD 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
PART I II III IV V

FIG. 2.

calcium balance on this régime; there was also a moderate positive phosphorus balance.

Part III. While continuing on the same régime as in Part II, the patient was given in addition 0·9 mg. of dienoestrol daily. The calcium balance became much more positive, the retention of calcium increasing by just over 1·1 gm. per period, due to a decrease in both the faecal and urinary excretion. There was no alteration in the positive phosphorus balance.

Part IV. The dose of dienoestrol was doubled to 1·8 mg. per diem. The calcium balance became still more positive, with an average retention of over 1·7 gm. of calcium per period. The positive phosphorus balance decreased slightly, due possibly to a reduction of 0·46 gm. per period in the phosphorus intake.

Part V. Vitamin D in a dose of 9,000 i.u. per diem was added to the régime given in Part IV to find out whether the patient, like Case 1, would give evidence of vitamin D deficiency. However, the calcium retention decreased somewhat, owing to an increase in the faecal calcium excretion. This increase is inexplicable except on the grounds that the parts of the experiment were too short to avoid being distorted by results, such as the abnormally high faecal calcium excretion in Period 26. But there was certainly no evidence that the patient was suffering from vitamin D deficiency. The positive phosphorus balance was unaltered from that in Part IV.

The actual phosphorus balance was considerably less positive than the theoretical balance throughout the experiment. From Fig. 6 it will be seen that the actual gain in weight slightly exceeded the theoretical gain, which suggests that there was an increase in extracellular fluid during the course of the experiment. The discrepancy cannot, therefore, be explained by loss of phosphorus through reduction in the volume of extracellular fluid. The changes in nitrogen balance appear to reflect changes in intake rather than any effect of oestrogen therapy. There were no significant changes in serum calcium, inorganic phosphorus, or alkaline phosphatase throughout the experiment.

Conclusions from Experiment 2

1. Dienoestrol given orally in a dose of 0·9 mg. daily along with a high calcium intake caused a significant increase in calcium retention, due to a decrease in both faecal and urinary calcium excretion. It was effective in promoting calcium retention in the absence of any supplementary vitamin D therapy. Doubling the dose of dienoestrol caused a further fall in faecal calcium excretion and hence an increase in the positive calcium balance.

2. There was no evidence of any effect of dienoestrol on the phosphorus and nitrogen balances.

Case 3. A married woman aged 68 years. Menopause at 49 years. There had been symptoms for two years before the start of the experiment.

In Experiments 1 and 2 the calcium/phosphorus ratio of the intake was abnormally high. In order to find out whether an increase in the phosphorus intake to give a calcium/phosphorus ratio approaching unity would increase the calcium retention, calcium glycerophosphate was substituted for calcium lactate in this experiment. Adams, Boothby, and Snell (1935) found that large doses of calcium lactate given to a woman with senescent (almost certainly postmenopausal) osteoporosis who was receiving a low phosphorus diet produced only a temporary increase in calcium retention, and they suggested that the low phosphorus intake was the limiting factor preventing continued retention of calcium. On the other hand, Anderson and Lyall (1939) found that in normal women a change from a high calcium and high phosphorus diet to a low phosphorus diet, in which the calcium intake was maintained at the previous high level with calcium lactate, decreased calcium retention over a 12-day experimental period in only one out of the three cases studied. In those parts of the present experiment with a high calcium and phosphorus intake a diet based on

the present rationing system was given; it contained an average of 0·623 gm. of calcium and 0·862 gm. of phosphorus per diem. Calcium glycerophosphate was used as a supplement in preference to tribasic calcium phosphate because its greater solubility permitted it to be given in solution, thus ensuring greater

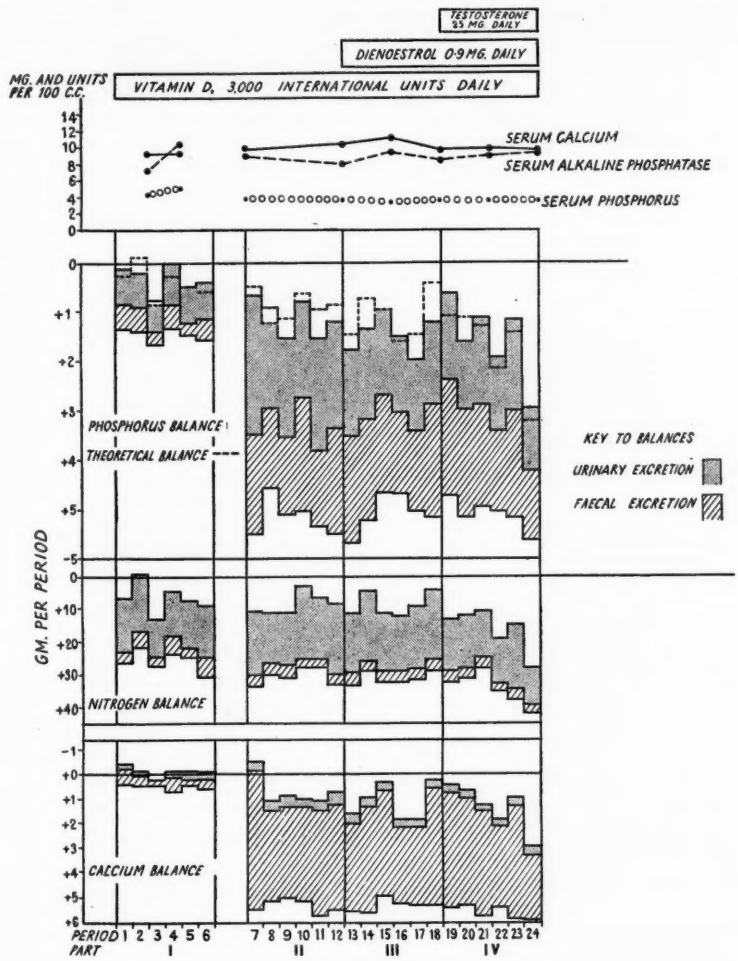
TESTOSTERONE 25 MG. DAILY
DIENOESTROL 0·9 MG. DAILY
VITAMIN D, 3,000 INTERNATIONAL UNITS DAILY
MG. AND UNITS PER 100 C.C.
SERUM CALCIUM
SERUM ALKALINE PHOSPHATASE
SERUM PHOSPHORUS
PHOSPHORUS BALANCE
THEORETICAL BALANCE
KEY TO BALANCES
URINARY EXCRETION
FAECAL EXCRETION
GM. PER PERIOD
NITROGEN BALANCE
CALCIUM BALANCE
PERIOD 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
PART I II III IV

FIG. 3.

accuracy of dosage. Sufficient of a 2 per cent. solution, the calcium and phosphorus contents of which were estimated by direct analysis, was given to bring the calcium content of the intake up to about 1·7 gm. daily; the phosphorus intake was thereby increased to almost the same figure. The experiment consisted of four parts, each comprising six three-day periods. The patient was given 3,000 i.u. of vitamin D daily to counteract any tendency to deficiency of this vitamin while in the ward. The metabolic data are shown in Fig. 3.

Part I. On the diagnostic low calcium diet, the faecal excretions of calcium

and phosphorus were within the range found in normal persons, but the urinary excretion of both substances was less, possibly owing to the amount of reduction in bone substance that had occurred in the long interval of time since the menopause.

Part II. On a high intake of both calcium and phosphorus, the patient went into well-marked positive calcium and phosphorus balance, the latter being rather greater than the theoretical balance. The urinary calcium excretion was much lower than in Cases 1 and 2 on a similar intake of calcium.

Part III. Dienoestrol, 0·9 mg. daily, was then given in addition to the high calcium and phosphorus intake. The positive calcium balance increased by 0·45 gm. per period; the increased retention was due entirely to a decrease in the faecal calcium excretion, there being no reduction in the already low urinary calcium output. The positive phosphorus balance also increased (by about 0·37 gm. per period) and was again slightly greater than the theoretical balance. The theoretical weight curve (see Fig. 6) did not reveal any tendency to retention of extracellular fluid to explain this discrepancy.

Part IV. Reifenstein and Albright (1947) demonstrated that testosterone propionate, when given in addition to oestrogen, promotes increased calcium retention in cases of postmenopausal osteoporosis, the maximum effect being reached after about 20 days of treatment. In Part IV, 25 mg. of testosterone propionate were injected intramuscularly every day, while the oral dose of 0·9 mg. of dienoestrol was continued.

There was an increase of 0·3 gm. per period in the calcium retention, but since the average calcium intake increased by this amount it is uncertain whether the increased retention can be attributed to the effect of testosterone. Injections of this hormone were given only for 18 days, and the marked increase in the positive calcium balance in Period 24 suggests that if testosterone therapy had been prolonged, a more significant effect on the calcium balance might have been demonstrated. There was a well-marked increase in nitrogen retention. The nitrogen intake was 3·5 gm. per period greater than in Part III, but the positive nitrogen balance increased by no less than 7·35 gm. per period. There was only an insignificant increase in the positive phosphorus balance, which in this part was somewhat less than the theoretical balance, in spite of the fact that the theoretical weight curve revealed no loss of extracellular fluid containing phosphorus. The results of the phosphorus balance are the more surprising in view of the considerable increase in nitrogen retention, and of the demonstration in both animal and human experiments (Thorn and Engel, 1938; Knowlton, Kenyon, Sandiford, Lotwin, and Fricker, 1942; Reifenstein and Albright, 1947) that testosterone propionate causes a prompt reduction in the excretion of phosphorus as well as of nitrogen.

There were no significant changes in the serum calcium, inorganic phosphorus, and alkaline phosphatase throughout the experiment.

Conclusions from Experiment 3

1. Increase of the phosphorus as well as the calcium intake did not increase the retention of calcium caused by administration of 0·9 mg. of dienoestrol daily above that found in Cases 1 and 2.

2. Calcium retention after the administration of dienoestrol is as great when the bulk of the calcium is given in the form of calcium glycerophosphate as when it is derived largely from dietary calcium.

3. Administration of testosterone propionate in addition to dienoestrol over a period of 18 days caused a marked retention of nitrogen, but had little or no effect on the calcium and phosphorus balances.

Case 4. A single woman aged 69 years. Menopause at 50 years. There had been symptoms for five years before the commencement of the experiment.

In the three preceding experiments the calcium intake used to demonstrate the effect of dienoestrol was about twice the accepted optimal figure. Reifenstein, Albright, and Wells (1945) emphasized that in studying the effect of oestrogen on the calcium balance, enough calcium should be given to permit a positive balance, but not so much that the expected improvement in the balance would be lost in the error of the experiment. In their experiments Reifenstein and Albright (1947) employed a calcium intake of about 0·7 gm. per diem. The object of the present experiment was to determine whether dienoestrol would promote a comparable degree of calcium retention on an intake of about 0·8 gm. per diem, as it was shown to do on an intake twice as great. The metabolic data are shown in Fig. 4.

Part I. On the diagnostic low calcium intake there was a gross negative calcium balance, due to excessive excretion in both urine and faeces.

Part II. To exclude the possibility that the high faecal calcium excretion in Part I was due to vitamin D deficiency, a supplement of 9,000 i.u. of vitamin D per diem was added to the low calcium diet. The average calcium intake was unfortunately somewhat lower than in Part I, and the negative calcium balance was rather greater. The faecal calcium excretion was actually greater than in Part I, in spite of the lower calcium intake and the vitamin D supplement, and it was concluded, therefore, that the excessive faecal calcium excretion could not be attributed to vitamin D deficiency. The actual phosphorus balance was negative in both parts, whereas theoretically it should have been positive.

Part III. The patient was then placed on a diet of normal calcium content (0·901 gm. per diem); vitamin D administration was continued in this and subsequent parts of the experiment at a level of 9,000 i.u. per diem. After six days to ensure equilibrium, metabolic studies were resumed. In spite of the optimal calcium intake there was still a gross negative calcium balance. The actual phosphorus balance was also negative, and more so than the theoretical balance.

Part IV. Dienoestrol in a dose of 0·9 mg. daily was added to the régime of Part 3. The negative calcium balance was practically eliminated by a reduction in both the urinary and faecal calcium excretion. There was a similar marked reduction in the negative phosphorus balance, but theoretically, in relation to the calcium and nitrogen balances, the phosphorus balance should have been positive.

Part V. The calcium and phosphorus intake was now raised to the high levels used in Case 3 by addition of calcium glycerophosphate solution to the intake. Dienoestrol therapy was continued at 0·9 mg. daily. Both the calcium and phosphorus balances became strongly positive, with retentions of over 0·5 gm. per period. However, there was a further fall in the urinary calcium excretion, which suggests the possibility that intensification of the effect of dienoestrol and not the high calcium and phosphorus intake may have been responsible for the improvement in the calcium balance. The actual phosphorus balance corresponded almost exactly with the theoretical balance.

Part VI. To investigate whether the high phosphorus intake contributed in any way to the improvement in the calcium balance, the phosphorus intake was reduced to that of Parts III and IV, while the calcium intake was maintained at

the same high level as in Part V by substituting the appropriate amount of calcium lactate for calcium glycerophosphate. This caused a decrease in the positive calcium balance due to an increased urinary calcium excretion, suggesting a decreased utilization of absorbed calcium. The phosphorus balance became negative again, to a greater extent than in Part IV. The urinary excretion was at

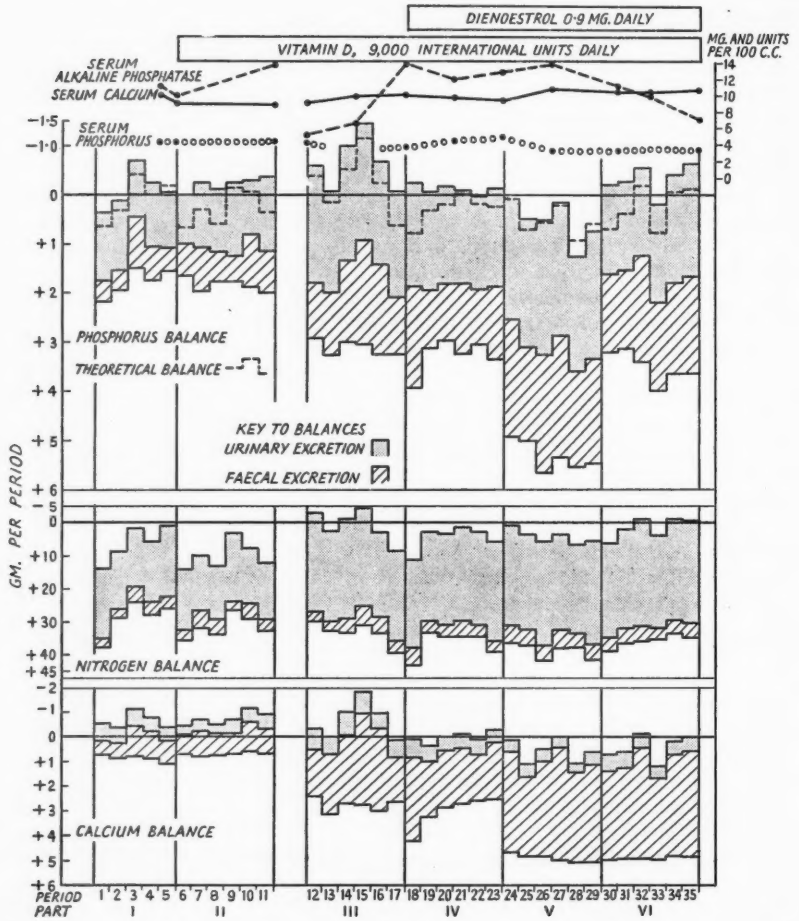

FIG. 4.

the same level as in Part IV, but there was an increased faecal excretion of phosphorus, presumably because of the increased calcium intake in Part VI as compared with Part IV. On theoretical grounds, the phosphorus balance should have been positive.

Throughout the whole experiment any variation in the consistently positive nitrogen balance appeared to be related to changes in the nitrogen intake rather than to any effect of dienoestrol therapy. There was no significant or consistent

change in the serum calcium, inorganic phosphorus, and alkaline phosphatase during the experiment.

Conclusions from Experiment 4

1. On a normal intake of calcium and phosphorus, dienoestrol promoted retention of these substances up to the point of almost eliminating gross negative balances, but without bringing about positive balances.

2. When a high calcium and phosphorus intake was given along with dienoestrol, a positive balance of both calcium and phosphorus resulted.

3. The degree of retention of calcium produced by dienoestrol appeared to be dependent to a certain extent on the level of intake of phosphorus.

4. Comparison of the actual and theoretical phosphorus balances suggests that there was a loss of phosphorus from sources other than bone or protoplasm, except when the phosphorus intake was high.

Case 5. A married woman aged 59 years. Surgical menopause at 49 years. Symptoms had commenced one year later.

The experiment consists of six parts—the first part (response to a low calcium diet) one year after the onset of symptoms, and the other five parts nine years after the onset of symptoms. The metabolic data are shown in Fig. 5.

Part I. On the low calcium diagnostic diet, there was an excessive negative calcium balance due to an increased excretion in both faeces and urine. The phosphorus balance was also more negative than in normal persons and more negative than the theoretical balance.

Part II. After an interval of eight years, further metabolic studies were carried out. The patient was first put on a high calcium and normal phosphorus intake (diet plus calcium lactate) with a supplement of 9,000 i.u. of vitamin D per diem. On this régime, there was an insignificantly negative calcium balance. The phosphorus balance was negative, whereas theoretically there should have been a considerable retention.

Part III. Dienoestrol, 0·9 mg. daily, was added to the above régime. The calcium balance became just positive, but the average calcium intake was greater by almost exactly the same amount as the improvement in the balance, and the only unequivocal evidence of an effect of dienoestrol was a reduction in the urinary excretion of calcium during the second half of this part. The phosphorus intake was lower; the negative phosphorus balance was increased to an even greater extent, although theoretically it should still have been positive.

Part IV. In an effort to improve the phosphorus balance, the patient was transferred to a diet moderately high in phosphorus. At the same time the calcium intake was reduced so as to give a calcium/phosphorus ratio of approximately unity, thereby avoiding interference with the intestinal absorption of phosphorus because of a calcium intake high in relation to that of phosphorus. On this régime, there was a moderate increase in calcium retention. The patient was in phosphorus equilibrium in this part of the experiment, but theoretically there should have been a retention of phosphorus.

Part V. In view of the finding in Case 4 that a high level of intake of both calcium and phosphorus appeared necessary to secure the maximal effect from dienoestrol therapy, the intake of calcium and phosphorus was increased to these high levels by the addition of calcium glycerophosphate to the diet given in Part IV. The intake of vitamin D was reduced to 3,000 i.u. per diem in Parts V

and VI. With the increased intake of calcium and phosphorus, there was a significant increase in the positive balance of both substances, and as in Case 4 on a similar régime, the actual and theoretical phosphorus balances showed reasonable correspondence. The patient had received dienoestrol for 36 days before the start of this part of the experiment. In view of the observation of

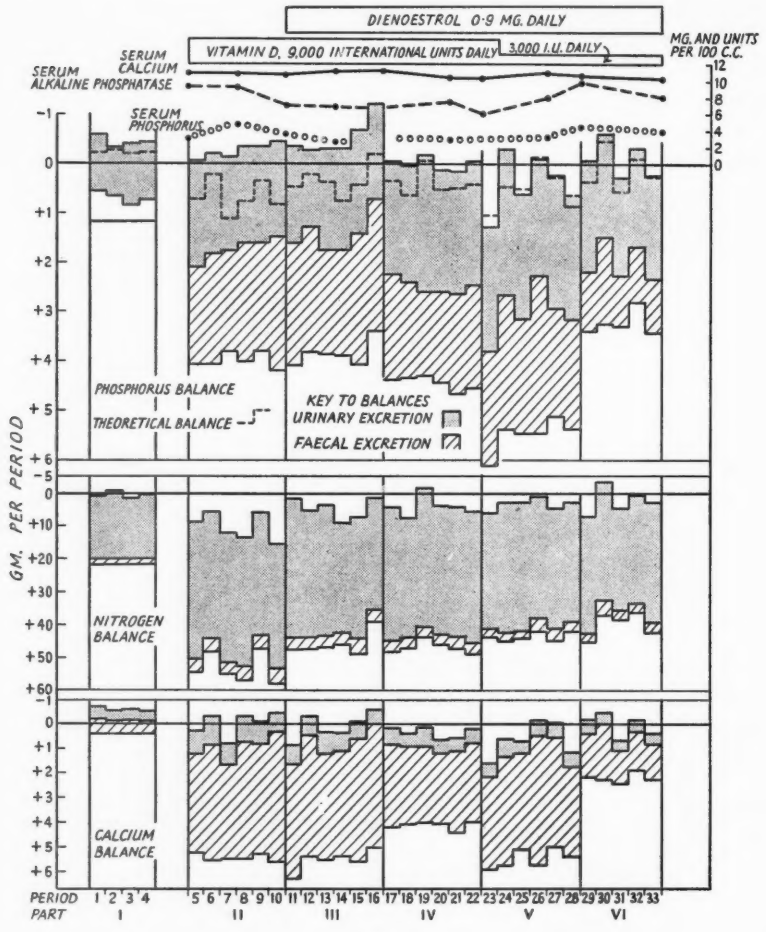

FIG. 5.

Reifenstein and Albright (1947) that the maximum effect of oestrogen therapy is not developed until after 30 days, it is possible that some, at least, of the improvement in the calcium and phosphorus balances may have been due to intensification of the action of dienoestrol. The fact that the urinary calcium excretion was lower than in Part IV, even though the calcium intake was higher, lends support to this suggestion.

Part VI. In Part VI of the experiment on Case 4, reduction of the high phosphorus intake diminished the action of dienoestrol in promoting calcium reten-

tion. The effect of a reduction in both the calcium and phosphorus intakes to normal levels was then studied. A great reduction occurred in the retention of calcium, about twice as great as in Case 4, when only the phosphorus intake was reduced. The fact that the urinary calcium excretion maintained the progressive decrease that had occurred since the administration of dienoestrol

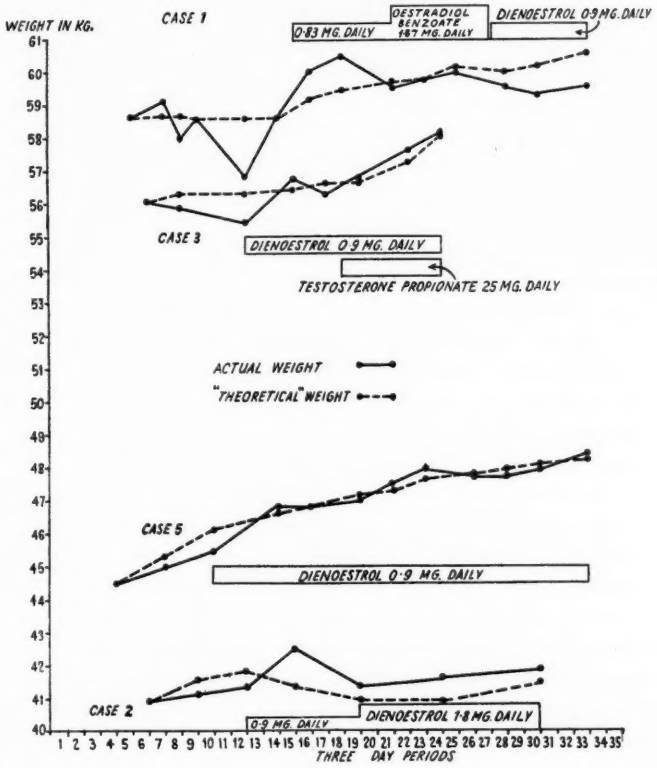

FIG. 6.

was begun suggests that this great fall in the positive calcium balance almost to zero was not due to any lessening of the effect of the oestrogen. The phosphorus balance became slightly negative, although theoretically there should still have been some retention of phosphorus.

As in the previous experiments, dienoestrol therapy produced no significant change in nitrogen balance, or in the levels of calcium, inorganic phosphorus, or alkaline phosphatase in the serum.

Conclusions from Experiment 5

1. As in Experiment 4, the greatest retention of calcium was secured when a high calcium and phosphorus intake was given along with dienoestrol.

2. Also, as in Experiment 4, comparison of the actual and theoretical phosphorus balances suggested that there was a loss of phosphorus other than from

bone and protoplasm unless a high phosphorus intake was given. The actual and theoretical weight curves (Fig. 6) are almost identical, so that there is no evidence of loss of phosphorus in extracellular fluid to explain the discrepancy between the actual and theoretical phosphorus balances.

Discussion

The action of dienoestrol in postmenopausal osteoporosis. The experiments described above indicate that the synthetic oestrogen, dienoestrol, has the same property of promoting the retention of calcium in cases of postmenopausal osteoporosis as the natural hormone, oestradiol. Certain differences in its action are apparent, however, when the present results are compared with those of Reifenstein and Albright (1947). These authors demonstrated that oestradiol benzoate caused significant retention of calcium and phosphorus when patients were receiving a normal intake of calcium (0·7 gm. per diem) and a low intake of phosphorus (0·51 gm. to 0·67 gm. per diem). In the present experiments, dienoestrol did not produce the same degree of retention of calcium unless the intake of calcium was high (about 1·7 gm. per diem), and furthermore, at this level of calcium intake, a phosphorus intake of about the same magnitude was necessary to secure such calcium retention in Cases 4 and 5. In the present experiments dienoestrol was given orally in about the same amount (0·9 mg. daily) as the intramuscular dose of oestradiol benzoate (0·83 mg. daily) used by Reifenstein and Albright (1947). Opinion regarding the oestrogenic potency of dienoestrol has altered since its introduction, and it is now considered to be less potent than either oestradiol or the synthetic oestrogen, diethylstilboestrol. This may explain the failure in the present experiments to secure a considerable degree of calcium retention except on a high calcium intake. But the implication that dienoestrol in weaker oestrogenic dosage can produce under such conditions as great and sometimes greater retention of calcium than oestradiol benzoate with a minimum of side-effects on the endometrium (see section on gynaecological effects) seems to be an argument in favour of its employment in the treatment of the skeletal lesions that may follow the menopause.

In an attempt to explain the requirement for a high phosphorus intake before the maximum effect of dienoestrol in promoting calcium retention could be secured, the theoretical phosphorus balance was calculated for each experiment. The results were inconclusive. In Cases 1 and 3 the actual phosphorus balance tended to be more positive than the theoretical balance. On the other hand, in Cases 2, 4, and 5 the actual balance was less positive than the theoretical, except where, in Cases 4 and 5, a high phosphorus intake was given, on which régime the actual and theoretical phosphorus balances showed reasonable agreement. Calculation of the theoretical weight curves (Fig. 6) gave no indication that the discrepancies between the actual and theoretical balances could be explained by retention or loss of phosphorus in extracellular fluids. Unfortunately, the effect of a high phosphorus intake on the retention of calcium produced by dienoestrol was not investigated in Cases 1 and 3, where the actual phosphorus balance was more positive than the theoretical balance. It must therefore be

left as a speculation whether the removal of the discrepancy between the actual and theoretical phosphorus balances and the improvement in the retention of calcium in Cases 4 and 5 when on a high phosphorus intake did, in fact, represent the correction of a metabolic aberration, with a resulting greater availability of phosphorus for deposition with calcium in the bones.

There was no indication that dienoestrol therapy increased nitrogen retention, and therefore no evidence of a protein anabolic action that stimulated the osteoblasts to lay down more protein bone matrix. Demonstration of such an effect would demand the histological examination of biopsy specimens of bone before and after treatment, which was not undertaken, but Sherman (1948) was able to demonstrate histologically in a patient with postmenopausal osteoporosis complicating Paget's disease of bone that intensive oestrogen therapy caused a generalized increase in the number and thickness of the previously atrophic bone trabeculae, with an increase in the number of osteoblasts and abnormally wide osteoid seams. A calcium balance could not be carried out, but a marked decrease in the urinary excretion occurred with dienoestrol therapy, and a subsequent increase when oestrogen was withdrawn.

In the present series, dienoestrol therapy caused a decrease in the excretion of calcium in the urine in all instances except Case 3, where the urinary calcium output was already low. This suggests that dienoestrol increased the retention of absorbed calcium, and the inference from Sherman's findings is that it did so by stimulating the osteoblasts to lay down more organic matrix in which calcium could be deposited. It is impossible to determine from the balance studies whether the fall in faecal calcium excretion that followed dienoestrol therapy in all patients except Case 5 was due to increased absorption from the intestine or decreased re-excretion into the intestine; from the concept of oestrogen action on bone developed by Albright the latter seems the more likely.

The demonstration that oestrogens cause hyperossification in male as well as female birds and some mammals suggests that their action on the osteoblasts in the human subject is not necessarily limited to conditions like that of postmenopausal osteoporosis, where endogenous production of oestrogens is deficient. Knowlton, Kenyon, Sandiford, Lotwin, and Fricker (1942) found that oestrogen caused retention of nitrogen and phosphorus in normal women, while Reifenstein and Albright (1947) showed that oestradiol benzoate promoted calcium retention in male cases of senile osteoporosis. Johnston (1941), however, found that in girls at or just before puberty, oestrogens tended to decrease rather than promote calcium retention. Further studies on the effect of oestrogens on the calcium balance in normal adult men and women are required before it can be decided whether or not their action on the osteoblasts is limited to cases with deficient endogenous production of oestrogens.

Clinical Results of Dienoestrol Therapy

Improvement in symptoms. On the whole, the clinical response to dienoestrol therapy was very satisfactory. All five patients obtained considerable relief from the back pain that had previously incapacitated them. The patients were

examined by Mr. A. M. Rennie, Senior Orthopaedic Surgeon to Aberdeen Royal Infirmary, who advised the wearing of a Goldthwaitt spinal brace in Cases 1, 3, and 4, in which there was collapse of vertebral bodies, in order to relieve pain and muscle spasm and to prevent the development of further pathological fractures. But Cases 2 and 5, patients who had no vertebral collapse and were not fitted with a spinal brace, also obtained relief on dienoestrol therapy, so that it seems evident that some of the amelioration of symptoms in Cases 1, 3, and 4 must have been due to dienoestrol. The extent of the relief of pain varied from patient to patient. Case 1, a patient who had been so severely incapacitated for about a year as to be partially bedridden, obtained considerable relief after six weeks' oestrogen therapy. After 18 months of dienoestrol therapy she was able to carry out her usual activities, the pain had completely disappeared, and she was able to dispense with the brace. Case 2 obtained considerable relief from, but not complete elimination of, symptoms within nine months of starting treatment. Case 3 admitted to amelioration, although not complete relief, of pain after six weeks' treatment with dienoestrol; there was still tenderness on palpation and percussion of the dorsal spine. After four and a half months' continuous therapy there was almost complete relief from pain, and the tenderness on percussion of the spine had disappeared; the patient was, however, still wearing a spinal support. Case 4 showed a gratifying response in that the back pain was completely relieved after five months' dienoestrol therapy and the wearing of a spinal brace, only a slight feeling of weakness in the back remaining. Case 5 obtained complete relief after five months' therapy without the use of a spinal brace.

Radiological examination. It is generally agreed that the radiological demonstration of differences in the density of bone at different times in the same patient is very difficult unless these differences are extreme. The conception that oestrogens increase the density of bone by stimulating the osteoblasts to lay down bone matrix in which calcium salts can then be deposited makes it understandable that this increase in density will be a more gradual process than the improvement in calcification brought about by restoration of the normal calcium and phosphorus content of the body fluids in rickets and osteomalacia. Reifenstein and Albright (1947) drew attention to this, and admitted that it had been difficult to secure unequivocal evidence that oestrogen therapy produced increased bone density, except, perhaps, in their longest-treated cases. Sherman's (1948) case was exceptional in that convincing radiological evidence of increased bone density was secured after only 28 days of intensive oestrogen therapy. In Case 1 the radiological reports after seven months of dienoestrol therapy contained guarded statements that there might be slight improvement in the density of the spine, but in none of the other cases after periods of up to one year from the commencement of treatment was there any radiological evidence of improvement.

Gynaecological effects. The prolonged administration of oestrogens that appears to be necessary in the treatment of postmenopausal osteoporosis carries with it the disadvantage of possible excessive oestrogenic stimulation of the

endometrium and resulting uterine haemorrhage. Reifenstein and Albright (1947) recommended that endometrial hyperplasia from oestrogen therapy should be controlled either by interrupting the therapy for one to two weeks every four to six weeks or by administering every four to six weeks a five days' course of progesterone or anhydrohydroxyprogesterone. Gynaecological supervision of the present series of cases was undertaken by Mr. A. Duncan, Senior Lecturer in the Department of Midwifery, University of Aberdeen. It was decided that in the first instance continuous therapy with dienoestrol should be carried out and the intensity of oestrogenic effect studied by periodical endometrial biopsies. The gynaecological history of Cases 1 to 4 follows (Case 5 had had a hysterectomy performed 10 years previously). All four patients were receiving 0·9 mg. dienoestrol per diem.

Case 1 had no uterine haemorrhage during the first nine months of treatment. She had a slight one-day haemorrhage in the ninth, tenth, and eleventh months; on the last occasion the uterus was reported to be larger than six months previously. Fourteen months after the start of therapy, uterine curettage was performed. The uterus was retroverted and enlarged. The cavity was irregular and several large polypoidal masses of endometrium were recovered. Histologically the endometrial glands showed well-marked hyperplasia and extensive cyst formation. Three months later, with no haemorrhages in the interval, a second uterine curettage was performed. The uterus was still enlarged, but the cavity was smooth and the scrapings only moderate in amount. Histologically, the endometrial glands were scattered and inactive, a few being somewhat dilated. It was considered that the endometrium showed no evidence of marked oestrogenic stimulation. At the time the patient was last seen, 20 months after therapy was commenced, there had been no further bleeding.

Case 2 had uterine haemorrhage lasting four days at the end of two months' therapy, at which time, however, she was receiving 1·8 mg. of dienoestrol per diem. Reduction of the dose to 0·9 mg. led to cessation of bleeding. For the next four months she had bleeding for three days every month. Three months later, there having been no further bleeding, uterine curettage was performed. The uterus was retroverted and enlarged. Histologically, the endometrium showed no glandular hyperplasia or other evidence of over-stimulation. The only further bleeding in the next seven months followed the unauthorized cessation of dienoestrol therapy, when there was a uterine haemorrhage lasting for a week. One year from the commencement of treatment a second uterine curettage was performed. The uterus was still enlarged, but otherwise there was nothing abnormal. Histologically, the endometrial glands were well developed and the lining cells showed elongation of the nuclei and well-marked subnuclear vacuolation. The latter was similar to the appearances seen in the progesterone phase of a normal menstrual cycle, but in a postmenopausal patient it was considered indicative of prolonged and unopposed oestrogen influence. In view of the histological evidence of regression of oestrogen over-stimulation in Case 1 with prolongation of dienoestrol therapy, it was decided that the treatment of Case 2 should be allowed to continue.

Case 3 had one slight uterine haemorrhage four months after starting dienoestrol therapy. The uterus was enlarged and slightly soft. Uterine curettage showed the cavity of the uterus to be somewhat irregular and the scrapings were fairly abundant. Histologically, the endometrium showed glandular hyperplasia, but almost no vacuolation of the cells. The condition was regarded as a variant of cystic glandular hyperplasia, and it was considered that there was no contra-indication to continuance of dienoestrol therapy.

Case 4 had had no uterine bleeding after five months' treatment with dienoestrol.

Prolonged administration of oestrogens to certain experimental animals is known to lead to the development of tumours in different organs, including the uterus. The possibility that oestrogens may have a similar effect in women must therefore be borne in mind, although so far there had been no direct evidence that such occurs. Reifenstein and Albright (1947) recommended that any uterine bleeding not associated with oestrogen or progesterone withdrawal should be investigated. In the present series such investigation has revealed no evidence suggestive of neoplastic change in the endometrium after continuous dienoestrol therapy for several months.

The Diagnosis of Postmenopausal Osteoporosis

There seems little doubt that postmenopausal osteoporosis is a definite disease entity. Furthermore, it does not appear to be a very rare disease. The five patients described above were admitted to the medical wards of the Aberdeen Royal Infirmary over a period of less than two years, and at least as many more cases were seen as out-patients and diagnosed as suffering from this condition by the process of exclusion mentioned below. The disease exposes the patient to a considerable degree of suffering and may be severely incapacitating. Oestrogen therapy appears to offer a means of ameliorating or even relieving completely the patient's subjective symptoms and possibly of leading to at least partial restoration of the structural stability of the bones. It is therefore desirable that the disease should be recognized and the appropriate treatment instituted, if possible before irreparable derangement of the vertebral bodies through collapse has occurred. Postmenopausal osteoporosis should be considered in the diagnosis of a complaint of pain in the back in a woman past the menopause, especially if there is a history of episodes of acute aggravation of the pain of the kind described earlier, and if radiological examination shows a diffuse osteoporosis affecting chiefly the spine and pelvis, with perhaps wedging and even collapse of one or more vertebral bodies. The time of onset of definite symptoms varies greatly. In Albright, Smith, and Richardson's (1941) series it occurred on the average about 10 years after the menopause. In the five patients considered in the present paper it ranged from one to 17 years after the menopause.

The laboratory investigations are characterized by the normality of the results. The blood chemistry shows normal levels of calcium, inorganic phos-

phorus, alkaline phosphatase and protein in the serum, and the albumin/globulin ratio is not altered. A tendency for the inorganic phosphorus to be near the upper limit of the normal range has been commented on (Meulengracht, 1939; Reifenstein and Albright, 1947), with a subsequent fall after oestrogen therapy, but none of the five cases in the present series showed this feature. The erythrocyte sedimentation rate is normal in the absence of some intercurrent condition. Diagnostic balance studies on a low calcium diet are not of great help, as the results seem to vary according to whether the patient is investigated early or late in the course of the disease. In the latter case the results, as judged by the present series, are likely to be normal, whereas in the early cases the balance may be excessively negative due to an increased excretion of calcium in the urine or in both urine and faeces.

Biopsy of bone is likely to be helpful only in the exclusion of other diseases of bone. The long bones, which are the most accessible for biopsy, are less affected in postmenopausal osteoporosis than are the spine and pelvis, and so are unlikely to show the striking changes described by Sherman (1948). In Case 5 of the present series a biopsy specimen taken from the tibia one year after the onset of symptoms, at a time when the diagnostic calcium balance on a low calcium diet was excessively negative and the osteoporotic process must therefore have been progressing, showed only a possible lessening of the number of bone trabeculae, but no abnormality of apposition or of resorption.

Before a diagnosis of postmenopausal osteoporosis can be accepted, other conditions leading to decreased density of the bones and to pathological fractures of vertebral bodies must be excluded. It is by such a process of exclusion rather than by any positive evidence from special investigations that the diagnosis of postmenopausal osteoporosis can finally be arrived at with some degree of certainty. Of other diseases associated with rarefaction of the spine, those that are most likely to cause difficulty are metastatic malignant disease involving the spine and the atypical forms of hyperparathyroidism and multiple myelomatosis in which, instead of the characteristic radiological appearances of these two diseases, there is only a diffuse rarefaction of the skeleton. In elderly patients the occurrence of a painful osteoporosis of the spine, especially if associated with pathological fracture of one or more vertebral bodies, inevitably raises the question of the presence of an osteoclastic type of metastatic malignant disease. While this usually gives a radiological picture of focal destruction with normal bone texture elsewhere, the bone destruction caused by the infiltration of malignant tumour cells may sometimes be more diffuse and uniform in its distribution, producing radiological appearances not unlike those of postmenopausal osteoporosis. Laboratory investigations of calcium and phosphorus metabolism are of no help in the differential diagnosis, which must depend on a careful search for a primary lesion whenever any symptoms suggest such a possibility. In hyperparathyroidism and multiple myelomatosis, the characteristic abnormalities of the blood chemistry may be helpful—the raised serum calcium and alkaline phosphatase and the decreased serum inorganic phosphorus of the former, and the hyperproteinaemia due to gross increase in globulin of the latter,

with sometimes hypercalcaemia (with a normal serum inorganic phosphorus and alkaline phosphatase) and a high serum uric acid. Bence-Jones proteinuria is an important although not pathognomonic feature of multiple myelomatosis, but occurs in only about 65 per cent. of cases, according to Geschickter and Copeland (1928). Balance studies on a low calcium diet may not always distinguish these conditions, for the excessive urinary excretion of calcium and phosphorus that characterizes hyperparathyroidism may also be found in multiple myelomatosis when hypercalcaemia is present and, as has been mentioned, an excessive urinary calcium excretion may sometimes be found in early cases of postmenopausal osteoporosis. Biopsy of a long bone in hyperparathyroidism and sternal puncture in multiple myelomatosis may be necessary before the diagnosis can be established. Since the latter disease can exist without any abnormality of the blood chemistry and without Bence-Jones proteinuria, sternal puncture is advisable before any patient showing rarefaction of the vertebrae is diagnosed and treated as one of postmenopausal osteoporosis; this procedure is essential where the erythrocyte sedimentation rate is raised.

Other diseases associated with spinal osteoporosis such as thyrotoxicosis, Cushing's syndrome, osteomalacia, and Paget's disease of bone involving only a few vertebrae are less likely to cause difficulty in diagnosis. The other clinical and biochemical manifestations of thyrotoxicosis and Cushing's syndrome are usually adequate to distinguish these diseases. In only one of the several conditions leading to osteomalacia—idiopathic steatorrhoea—is the onset of symptoms likely to be delayed until well on in adult life, and other manifestations of this disease are likely to be present; the blood chemistry may be helpful in diagnosis, for when osteomalacia has progressed to a stage capable of clinical and radiological recognition, there is likely to be a low inorganic phosphorus, a normal or low calcium, and a raised alkaline phosphatase in the serum. Fat-balance studies on the lines recommended by Cooke, Elkes, Frazer, Parkes, Peeney, Sammons, and Thomas (1946) should be made if there is any doubt as to the presence of idiopathic steatorrhoea. Paget's disease of bone can usually be excluded on radiological grounds, and the high serum alkaline phosphatase with normal calcium and inorganic phosphorus that is found in this condition contrasts with the normal level existing in postmenopausal osteoporosis. The distinguishing features in the laboratory investigation of the more important causes of rarefaction of the spine are summarized below.

The Treatment of Postmenopausal Osteoporosis

The management of a case of postmenopausal osteoporosis has three objects: to relieve pain, to restore the structural stability of the bones, and to prevent further deformity of the vertebral bodies. The experiments described above suggest that treatment with the synthetic oestrogen, dienoestrol, supplemented by a high calcium and phosphorus intake will achieve the first of these objects, and perhaps the second. Orthopaedic measures are required for the third. Therapy should therefore include the following procedures.

Administration of oestrogen. From the present experiments it appears that dienoestrol in a dose of 0·9 mg. daily is as effective as injection of oestradiol benzoate, if given together with a high calcium and phosphorus intake, and is unlikely to cause uterine bleeding of such severity as to make its continued administration undesirable. Present experience suggests that courses of progesterone to prevent oestrogen over-stimulation of the endometrium are not

	Blood chemistry						
Disease	*Calcium*	*Phosphorus*	*Phosphatase*	*Protein*	*Calcium balance*	*Sternal puncture*	*Bone biopsy*
Postmenopausal osteoporosis	N	N	N	N	N or −	N	? N
Metastatic malignant disease	N or +	N	N or +	N	N	N	N
Hyperparathyroidism	+	−	+	N	−	N	Osteitis fibrosa
Multiple myelomatosis	N or +	N	N	+	N or −	+	N
Paget's disease	N	N	++	N	N	N	N or +
Osteomalacia due to steatorrhoea	N or −	−	+	N	− (excess Ca in faeces)	N	Osteomalacia

N = normal. In the calcium balance column, N means that on a low calcium diet the calcium balance is no more negative than in a normal person, and a minus sign indicates that the balance is excessively negative.

necessary at this level of dienoestrol dosage. The question of how long oestrogen therapy should be continued after symptomatic relief of pain is one that is difficult to answer at present, but it is clear that restoration of normal structural stability of the bones, if, in fact, this can ever be secured, will be a matter of years rather than months.

A high calcium and phosphorus intake. To ensure the maximal effect on calcium retention of dienoestrol in the dose recommended, it seems essential that a calcium and phosphorus intake of about twice the normal levels must be given. This does not call for special dietetic measures, and the easiest way of securing this high intake is by the administration of calcium glycerophosphate in powder form in a dose of 30 gr. (approximately 2 gm.) thrice daily to supplement a normal diet.

Vitamin D. There is no evidence that vitamin D augments the effect of oestrogens on calcium retention, but many of the patients will have been more or less confined indoors for a prolonged period. It therefore seems advisable to prescribe vitamin D in a moderate dose (up to 10,000 i.u. per diem) to relieve any deficiency that may have developed. The results in Case 1 suggest that this may sometimes prove beneficial.

Orthopaedic treatment. The employment of some form of spinal support in patients with collapse of vertebral bodies and muscular spasm seems logical, but as Reifenstein and Albright (1947) have pointed out, prolonged immobilization should be avoided because of the danger of superimposed disuse atrophy of bone. Therefore, the use of the spinal support should be omitted gradually when the back pain has been relieved. The patient must be warned against undue physical exertion or sudden movements during this period.

Summary

1. The synthetic oestrogen, dienoestrol, has a metabolic effect similar to that of the natural oestrogen, oestradiol, in promoting calcium retention in women suffering from postmenopausal osteoporosis. In the dose used, the effect appears to be maximal only if the calcium and phosphorus intakes are both about twice the accepted optimal requirement. It has a similar but less striking effect on phosphorus retention, and no significant effect on nitrogen balance.

2. Dienoestrol therapy produces amelioration of the subjective symptoms. Unequivocal radiological evidence of increase in the density of the bones has not been obtained.

3. The diagnosis rests on the history, the normality of the results of laboratory investigations, and chiefly on the exclusion of other causes of rarefaction of the spine.

4. The suggested treatment includes the administration of dienoestrol, vitamin D, and calcium glycerophosphate to secure a high calcium and phosphorus intake. Protective orthopaedic treatment is indicated in cases with collapse of vertebral bodies.

Note

In Figs. 1 to 5:

(1) Intakes are plotted downwards from the zero base line. Excretions, divided into faecal and urinary components, are plotted upwards from the bottom of the intake area. The balance between intake and excretion is therefore read off from same zero base line irrespective of variations in intake.

(2) Units of the scales for calcium, phosphorus, and nitrogen express the metabolic relationships between these substances. One phosphorus unit = 15 nitrogen units (nitrogen/phosphorus ratio in soft tissues approximately 15/1). One phosphorus unit = 2 calcium units (calcium/phosphorus ratio in bone approximately 2/1). Areas on charts representing balances can therefore be compared directly with one another.

I wish to express my thanks to the following members of the staff of Aberdeen Royal Infirmary: Professor H. W. Fullerton, Professor John Craig, and Dr. Ian Gordon for permission to investigate Case 1, Case 3, and Cases 2 and 4 respectively; to Dr. D. P. Levack for the radiological investigations; to Mr. A. M. Rennie and Mr. A. Duncan for their kindness in supervising the orthopaedic and gynaecological aspects of treatment; and to Dr. A. Lyall for affording me facilities in the Metabolic Ward of Aberdeen Royal Infirmary. I am glad to acknowledge invaluable help from Sister M. E. Thomson of the Metabolic Ward in the construction and preparation of the diets and in supervision of the collection of material. I am indebted to Mr. George Cheyne and Mr. A. Brand for valuable technical assistance.

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APPENDIX

Case Reports

Case 1. A single woman, aged 48 years. Menopause at 42 years. Four years later she developed a severe pain in her back while using a mangle. The pain was aggravated by bending and on lifting weights. Radiological examination showed severe decalcification of the spine, and to a less extent of the peripheral bones. There was multiple collapse of vertebral bodies, including the fifth, eighth, and tenth dorsal, and the third and fourth lumbar vertebrae (Plate 9, Fig. 7). She was treated with a high calcium intake plus vitamin D, with little effect at first, but with apparent amelioration of pain later. A year after, on turning round suddenly, she 'felt something snap' in her back and was seized with severe pain. For the next year up to the time of admission she was more or less confined to the house with pain in the back and left hip, which was aggravated on moving her left leg. Her general health was good and she had no other complaints. Physical examination was essentially negative, except that the lumbar spine was kept rigid by muscle spasm. There was a moderate rounded

dorsal kyphosis, but no angulation. All movements of the spine were restricted and painful, but there was no local tenderness on palpation or percussion. Urine analysis was normal. Radiological examination showed, in addition to the appearances noted before, that the left borders of the ninth, tenth, and eleventh dorsal vertebrae were missing, this local erosion of bone suggesting a neoplastic origin for the general bone picture.

Laboratory investigations. Sternal puncture—marrow normal. Blood count—red and white cell counts and blood-film normal. Serum-calcium 10·0 mg. per 100 c.c. Serum inorganic phosphorus 3·7 mg. per 100 c.c. Serum alkaline phosphatase 5 King-Armstrong units per 100 c.c. Blood-urea 38 mg. per 100 c.c. Blood uric acid 1·8 mg. per 100 c.c. Plasma-proteins 7·12 gm. per 100 c.c. (albumin 3·75 gm., globulin 3·37 gm.). Urea clearance (standard) 73 per cent. of normal. Excretion of fat in faeces over three-day period on intake of 90 gm. of fat per diem was 1·8 per cent. of intake. A fractional test meal showed no free hydrochloric acid in early specimens, but later a normal content.

Case 2. A single woman, aged 65 years. Menopause at 50 years. Two years after the menopause she began to suffer from aching pain in the left scapular region, aggravated by bending and during cold weather. Seven years later she became aware of deformity of the back, with undue prominence of the left side of the back. One year later she began to suffer from sharp shooting pains in the lower thoracic region. Pains in the left shoulder and back had been continuous since then. There were no other complaints apart from dyspepsia. Physical examination revealed a considerable fixed kypho-scoliosis of the cervico-dorsal region with convexity to the left and rotation of the transverse processes of the cervical and upper dorsal vertebrae on the left side. The lower thoracic and lumbar regions showed a compensatory lordo-scoliosis with convexity to the right. There was no localized tenderness on palpation or percussion of the spine. The urine was normal. Radiological examination showed the gross kypho-scoliosis of the upper dorsal spine with the usual static deformity of the affected vertebrae, but no localized rarefaction. The whole skeleton, especially the spine and pelvis, showed a moderate generalized decalcification.

Laboratory investigations. Sternal puncture—marrow normal. Blood count showed the presence of a mild hypochromic anaemia. Serum-calcium 9·4 mg. per 100 c.c. Serum inorganic phosphorus 3·8 mg. per 100 c.c. Serum alkaline phosphatase 16 King-Armstrong units per 100 c.c. Blood-urea 29 mg. per 100 c.c. Blood uric acid 3·1 mg. per 100 c.c. Plasma-proteins 6·4 gm. per 100 c.c. (albumin 3·0 gm., globulin 3·4 gm.). Urea clearance (standard) 80 per cent. of normal.

Case 3. A married woman aged 68 years. Menopause at 49 years. The patient was in good health up to two years before the present study, when she felt a sudden snapping sensation in her left side, which was followed by pain in the left iliac fossa and paraesthesia of the left leg. She was first admitted to hospital four months after the onset of symptoms. There was no demonstrable abnormality on physical examination, but radiologically there was generalized decalcification of the lumbar spine with biconcavity of vertebral bodies and collapse of the body of the third lumbar vertebra. The lesion was considered to be characteristic of a metabolic calcium deficiency. The patient was discharged on a high calcium intake plus vitamin D. A few weeks later she developed an acute pain in the left loin on straightening up suddenly. The pain later settled in the lumbar spine; it gradually became less severe with rest in bed, and on her second admission to hospital, 18 months after the first onset of symptoms, the pain was dull and aching, but was aggravated by weight-lifting. Physical

examination showed a marked dorso-lumbar kyphosis, with moderate restriction of all spinal movements and pain on extension. There was tenderness on palpation and percussion in the lower dorsal region. The urine was normal. Radiological examination revealed a collapse of the bodies of the eighth and tenth dorsal vertebrae, without evidence of local erosion. The rest of the skeleton, including the skull, showed a moderate decalcification (Plate 9, Fig. 8).

Laboratory investigations. Blood count and film normal. Erythrocyte sedimentation rate (Westergren) 4 mm. in one hour. Sternal puncture—no myeloma cells seen in sternal marrow. Fractional test meal—no free hydrochloric acid until injection of histamine, which elicited acid secretion. Serum-calcium 10·9 mg. per 100 c.c. Serum inorganic phosphorus 3·3 mg. per 100 c.c. Serum alkaline phosphatase 13 King-Armstrong units per 100 c.c. Plasma-proteins 7·0 gm. per 100 c.c. (albumin 4·3 gm., globulin 2·7 gm.). Urea clearance (standard) 69 per cent. of normal. Excretion of fat in the faeces during a three-day period on an intake of 90 gm. of fat per diem was 2 per cent. of intake.

Case 4. Single woman, aged 69 years. Menopause at 50 years. Five years before admission she had begun to suffer from weakness and vague pain in the lower part of the back. A month before admission, while stooping to open a drawer, she had been seized with severe pain in the back, which lasted for several days and for which she had to stay in bed. The pain became less and she was able to get up, but aching pain persisted up to the time of admission. On physical examination there was a prominent angular kyphosis at the dorso-lumbar junction, and the spine at the site of the kyphosis and for some distance above was tender on palpation and percussion. Movements of the spine were not greatly restricted, but extension was painful. Physical examination was otherwise negative. The urine showed no abnormality. Radiological examination showed generalized osteoporosis of the skull, long bones, spine, and pelvis, which was very advanced in the spine. There was advanced hypertrophic arthritis of the dorsal spine and collapse of the bodies of the tenth and eleventh dorsal vertebrae. Apart from the loss of calcium the structure of the bones was normal, and there was no evidence of cyst formation or erosive disease (Plate 10, Fig. 9).

Laboratory investigations. Sternal puncture—normal marrow smear. Serum-calcium 9·8 mg. per 100 c.c. Serum inorganic phosphorus 4·4 mg. per 100 c.c. Serum alkaline phosphatase 9 King-Armstrong units per 100 c.c. Blood-urea 30 mg. per 100 c.c. Blood uric acid 1·6 mg. per 100 c.c. Plasma-proteins 6·6 gm. per 100 c.c. (albumin 3·9 gm., globulin 2·7 gm.). Excretion of fat in faeces over nine-day period on an intake of 67 gm. of fat per diem was 2·3 per cent. of fat intake.

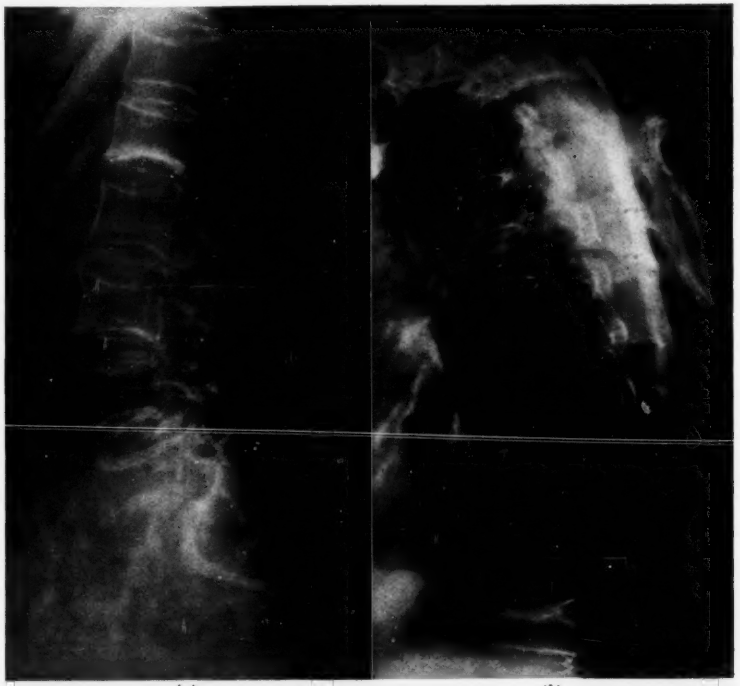
Case 5. A married woman, aged 59 years. Surgical menopause at 49 years. About a year later she developed pain in the left shoulder, neck, and lower part of the back. She was able to continue with her household duties, but was easily tired. She had noticed that bony parts were painful to the touch. On admission, physical examination revealed nothing abnormal except for marked tenderness on firm palpation of the lumbar vertebrae, and indeed of any bone. The urine showed a faint trace of albumin; the urinary deposit contained an excess of leucocytes and bacteria, but no red blood cells or casts. Radiological examination showed generalized osteoporosis of the spine and peripheral bones.

Laboratory investigations. Blood count normal. Serum-calcium 11·0 to 11·6 mg. per 100 c.c. Serum inorganic phosphorus 3·5 to 3·9 mg. per 100 c.c. Serum alkaline phosphatase 14 to 17 King-Armstrong units per 100 c.c. Blood-urea

44 mg. per 100 c.c. Plasma-proteins 6·7 gm. per 100 c.c. (albumin 3·9 gm., globulin 2·8 gm.). Urea clearance (standard) 54 per cent. of normal.

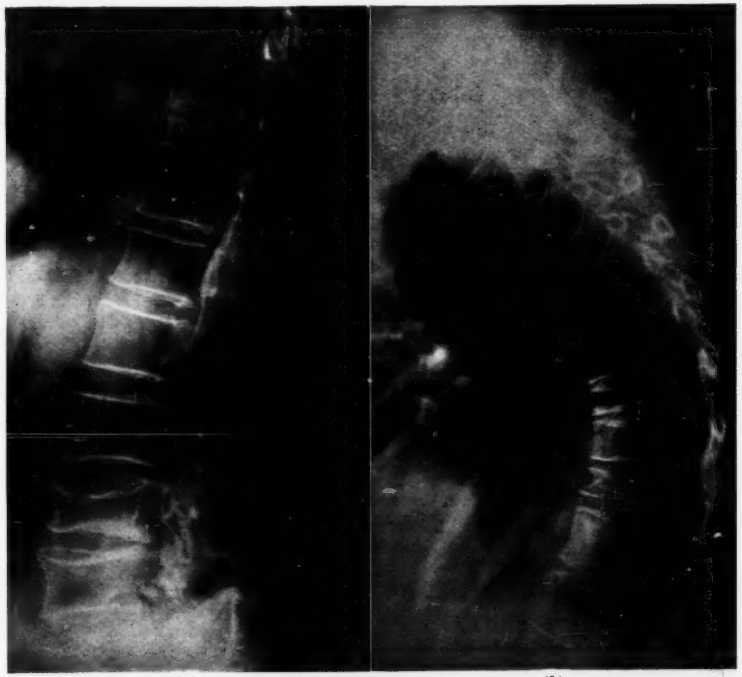
Tibial biopsy showed reduction in number of bone trabeculae, but no evidence of increased osteogenesis or osteolysis. The metabolic study given in Part I of Fig. 5 was carried out. No diagnosis of the cause of the osteoporosis was made, and she was discharged on a high calcium intake with added vitamin D. The patient continued to have vague aching pains in the back and felt easily tired, in spite of continued calcium and vitamin D therapy. Eight years later, when the present experiments were being carried out, it was decided to try the effect of oestrogen therapy. Physical examination revealed no change in her condition, and radiological examination showed that there was no apparent difference in the degree of osteoporosis as compared with the previous films.

Laboratory investigations on second admission. Serum-calcium 10·4 mg. per 100 c.c. Serum inorganic phosphorus 3·2 mg. per 100 c.c. Serum alkaline phosphatase 11 King-Armstrong units per 100 c.c. Blood-urea 45 mg. per 100 c.c. Urea clearance (standard) 37 per cent. of normal. Excretion of fat in faeces over a three-day period on an intake of 115 gm. of fat per diem was 7 per cent. of fat intake.



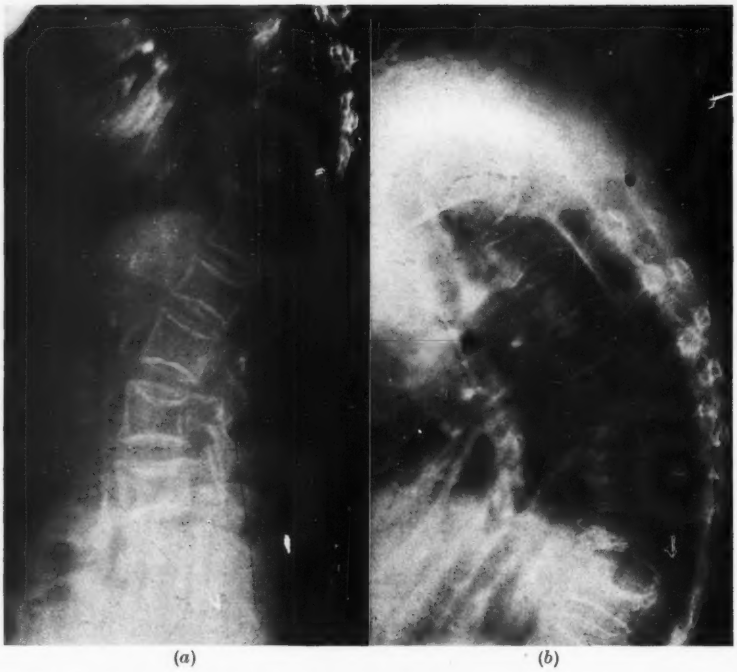
(*a*) (*b*)

FIG. 7. *Case 1.* (*a*) Lumbar spine, showing extreme decalcification, and partial collapse of the bodies of the third, fourth, and fifth lumbar vertebrae.
(*b*) Thoracic spine, showing decalcification and excessive biconcavity of the bodies of the vertebrae.



(*a*) (*b*)

FIG. 8. *Case 3.* (*a*) Lumbar spine, showing decalcification, and partial collapse of the bodies of the third and fourth lumbar vertebrae.
(*b*) Thoracic spine, showing wedging of the bodies of the eight and tenth thoracic vertebrae.



(*a*) (*b*)

FIG. 9. *Case 4.* (*a*) Lumbar spine, showing extreme decalcification and excessive biconcavity of the bodies of the vertebrae.
(*b*) Thoracic spine, showing collapse of the bodies of the tenth and eleventh thoracic vertebrae.

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THE ASSOCIATION OF BRONCHIAL CARCINOMA AND PERIPHERAL NEURITIS[1]

By Bernard Lennox and Stobo Prichard

(From the Departments of Pathology and Medicine of the Postgraduate Medical School, Ducane Road, London, W. 12)

With Plates 11 and 12

The more improbable a syndrome, the more necessary is its study; and the present subject admirably fulfils this criterion. A great deal has been written about carcinoma of the lung, and probably even more about peripheral neuritis, but nothing to suggest that they should occur together except by simple coincidence. If such an association can be proved, then a gap in our knowledge of both of these common and important conditions becomes obvious.

The first case of such an association was demonstrated to the Royal Society of Medicine by Dr. D. Kendall, and later by Professor Denny-Brown, in 1939. Nothing was published, however, until 1948, when Wyburn-Mason reported three cases, including the original one. Later in the same year Denny-Brown reported two of these cases independently in considerably greater detail, and showed that the nervous changes in both were of an unusual type. This seems to be the whole literature on the subject. Meerloo (1944) described nine cases of an 'initial neurologic and psychiatric syndrome of pulmonary growth', and some of these may have had peripheral neuritis; but the clinical descriptions are brief, no autopsies are described, and he does not seem to have attempted to exclude brachial plexus metastasis or vertebral lesions. Camäuer (1945), in the most recent review of the neurological complications of carcinoma of the lung, does not mention peripheral neuritis. One of his cases, presented as an example of onset by cerebral metastasis, also had peripheral neuritis, but this may have been, as Camäuer supposed, of alcoholic origin.

Our own interest was aroused by the occurrence of two cases (1 and 2 in the present series) almost simultaneously. It seemed to us that the relatively large number of cases of carcinoma of the lung which pass through the wards of a general hospital affords the best opportunity of testing the truth of the assumption that this association is not purely fortuitous. Hammersmith Hospital, with its London County Council origins and its active radiotherapeutic department, probably sees more bronchial carcinoma than most; and though, through a change in the filing system, our study was confined to the past eight years, we were able to collect 299 instances of that disease in which adequate records were available. These included three more cases of peripheral neuritis, making

[1] Received September 21, 1949.

five in all. The significance of this 1·7 per cent. incidence will be examined after description of our five cases.

Case 1

A married man of 38, a furrier, had had, 12 years before admission, an episode in which, immediately after an attack of 'influenza', his legs became weak and he felt unsteady. His arms then became weak, he was unable to do up buttons, and his writing became large and untidy. He could not remember suffering from numbness or paraesthesia. He recovered completely in 14 weeks. Unfortunately, the records of the institution at which he was treated were destroyed during the war, and no objective account was obtainable. Four years later he was passed fit (Grade 1) for the National Fire Service. Twelve weeks before admission he began to have a cough, which produced a little greyish sputum. He was becoming breathless on exertion. Three weeks later he complained of loss of energy, failure of appetite, nausea, and some general malaise. His legs felt weak and, at the same time, a 'numb' feeling appeared in the palms of his hands and in his feet. Everything he touched felt 'rough'. These symptoms gradually progressed during the next two weeks, until he had difficulty in walking. Six weeks before admission he coughed up about two drachms of dark-red blood, and his sputum was tinged with blood for the next few days. Shortly afterwards his legs got stronger again, until he was able to walk almost normally. He took no alcohol, and there were no occupational hazards. His diet was full, and he took no drugs.

On examination, he was a thin man, with no evidence of dietary deficiency and no finger clubbing. His mental state and cranial nerves were normal. The limbs were hypotonic and flabby, with some generalized weakness which was more obvious peripherally. There were no sensory disturbances in his arms, but there was slight vibration loss in his feet. All the tendon-reflexes were absent; the plantar responses were flexor. Romberg's test was negative. There was evidence of collapse of the lower lobe of the left lung. The cardiovascular system and the abdomen were normal. Chest X-ray, bronchoscopy, and biopsy confirmed the presence of a squamous carcinoma of the left main bronchus. The cerebrospinal fluid contained no cells, and 30 mg. of protein per 100 ml. The Lange gold curve was 1111000000. The Wassermann reaction was negative in blood and cerebrospinal fluid. A blood count was normal.

During the first month in hospital, the polyneuritis improved, his legs became stronger, and the biceps-jerks could be obtained. A left pneumonectomy was carried out by Mr. A. M. McArthur. At operation it was evident that a small portion of the growth had to be left behind, but it was considered that the palliative effect of pneumonectomy was worth while. The post-operative course was stormy, but 10 days later he was beginning to walk about the ward. The central nervous condition was unchanged, except that he had developed a traumatic left vocal cord paralysis. There was a left pleural effusion, but otherwise his chest condition seemed to be satisfactory. He had no pyrexia. Five weeks after operation there was a sudden deterioration in his polyneuritis, not associated with any obvious change in his chest. He complained of numbness of his extremities, and was much weaker. He now had some peripheral sensory loss, particularly to posture and vibration. From this time he gradually went downhill. The polyneuritis became very severe, and affected his face and trunk muscles as well as his limbs, and he became unable to move his legs below the knee. The sensory loss progressed. The diaphragm became paralysed. He was unable to cough. He developed broncho-pneumonia, and died four months after admission.

Autopsy. The left lung had been removed, the mediastinum was shifted over to the left, and the apex of the heart was adherent to the inside of the operative incision. Small tumour nodules were found in the pleura, pericardium, and mediastinal lymph-nodes, but the total amount of tumour present was not more than 5–10 gm. The middle and lower lobes of the right lung were collapsed, and their bronchi stuffed with thick mucopus. The remaining viscera showed no important lesion. The nervous system was macroscopically normal throughout. No trace of tumour was seen anywhere outside the thorax. In view of the microscopic findings in the right phrenic nerve, it is important to note that it was dissected out in all its thoracic course, and was quite free from tumour. Microscopically, the tumour was an ill-differentiated squamous carcinoma (Plate 11, Fig. 1). Nothing else of note was seen in the viscera, apart from the nervous system. Sections of frontal cortex, internal capsule, and mamillary bodies showed no abnormality. Blocks of the spinal cord were cut at five levels for formalin and Weigert-Pal fixation, and at each level the meninges and nerve-roots were preserved as nearly as possible intact (Plate 11, Figs. 2, 3, and 4). No lesion was found in the cord itself. In the upper thoracic region (Fig. 3) a group of three roots shows demyelinization. The group has unfortunately been displaced, and it is not possible to say with certainty whether they are anterior or posterior roots. Their relation to the meninges suggests a posterior origin, but the complete lack of demyelinization of the posterior columns speaks rather for the anterior. No posterior root ganglia were examined, but the lack of lesions in the posterior columns, and their absence, or at least scarcity, in the posterior roots, is strong evidence against any extensive lesion there.

Much more striking lesions were seen in the peripheral nerves. The sciatic nerve, sectioned in mid-thigh (Plate 12, Figs. 5, 6), shows demyelinization of some fibres in all bundles, and of all fibres in some. Only the slightest of cellular reactions has occurred, and the axons (Bodian's method) appear intact. The anterior tibial nerve in mid-leg is less affected, and an interdigital nerve of the foot (Plate 12, Fig. 7), chosen as being as nearly as possible a purely sensory nerve, is almost unaffected. The right phrenic nerve (Plate 12, Fig. 8) is severely affected, with hardly an intact fibre. The muscle of the diaphragm appeared normal, the tibialis anterior moderately atrophic, the peronaeus tertius markedly so. These changes do not correspond to the degree of paralysis present, but approximately to its duration, and suggest strongly that the lesions are entirely secondary. No satisfactory impregnation of nerve endings was achieved, but from the available evidence it seems improbable that the polymyositis described by Denny-Brown (1948) was present.

Summary of Case 1. A man of 38 had had a previous attack of polyneuritis 12 years earlier. He was admitted with moderately severe peripheral neuritis of two months' duration; he had had chest symptoms for a little longer. A squamous carcinoma of the left main bronchus was found, and palliative pneumonectomy performed. His neuritis, which had begun to improve before operation, relapsed suddenly six weeks after it, and he died from diaphragmatic paralysis. At post-mortem the nervous lesion was shown to be a demyelinization of peripheral nerves, chiefly motor. Only a small amount of recurrent tumour was present.

Case 2

This man, an old-age pensioner aged 66 years, had been feeling well until three weeks before he was first seen, when he noticed that his legs were becoming

weak. Over the next few days the symptoms progressed, until he had difficulty in walking. He would trip over the kerb, and his toes would catch in mats on the floor. At the same time he noticed symmetrical numbness and pins-and-needles in both his legs, and in his hands. A day or two later he found that his vision was becoming blurred for near objects, to such an extent that he had difficulty in reading a newspaper. Two weeks later he began to improve a little until, on the day he attended hospital, he said that his legs were almost as strong as usual, although he still had some numbness and paraesthesia. He had no cough and no dyspnoea. He thought he had lost two or three pounds in weight during the previous three weeks. His appetite was good. He had suffered from a winter cough for 20 years, but had otherwise always been a healthy man. There was no relevant family history. He had an occasional glass of beer, and smoked about one ounce of tobacco a week. His diet was adequate. He took no drugs.

On examination, he was a well-built man who looked in fair health. There was no clinical abnormality of his lungs, heart, or abdomen. The blood-pressure was 160/90. He was mentally alert, but rather slow. His pupils reacted sluggishly to light and accommodation. The left side of his face moved rather better than the right. He had a fine tremor of the hands; the arms were hypotonic, and there was very slight weakness of a peripheral type. There was no loss of sensation. The biceps- and supinator-jerks were absent; the triceps-jerks could be obtained with reinforcement. His abdominal reflexes were present. The legs showed slight peripheral weakness. The leg tendon-reflexes could be obtained with reinforcement, except for the right ankle-jerk, which was absent. The plantar responses were flexor; there was no sensory loss. A full blood count was normal. We considered that he was recovering from a mild polyneuritis. He was given vitamin B by mouth. When he was seen again a fortnight later, he was feeling much better and all his reflexes, with the exception of the left biceps-jerk, could be obtained.

During the next six months he remained fairly well, although he had bouts of paraesthesia lasting a few days, and lost more weight. On subsequent examination he looked unwell, and, though there were no abnormal signs, his chest was X-rayed, revealing an opacity in the left upper zone. He was admitted to hospital, where the diagnosis was confirmed of an inoperable carcinoma of the left upper bronchus. Neurological examination now revealed sluggish ankle-jerks as the only abnormality. He was given deep X-ray therapy, with a good local result. For a further six months he continued to have bouts of paraesthesia in his hands and legs. Towards the latter part of that time his legs became much weaker. On examination, there was moderate wasting of the muscles of his hands, forearms, and legs, with corresponding weakness. All the reflexes could just be obtained with reinforcement, except for the supinator-jerks. There was no sensory loss. During the next two months he developed evidence of secondary deposits in his brain, and he lapsed into coma and died.

Autopsy. The upper lobe of the left lung was densely fibrosed, and contained in its centre a rounded nodule 20 mm. in diameter. This nodule was almost certainly a peripheral recurrence, and not the original tumour, whose site could be traced as a fibrous stricture of the main bronchus to the lobe near its origin. The lower lobes of both lungs showed bronchopneumonia. In the brain there were three cystic metastases, each about 30 mm. in diameter, two in the right frontal and one in the left occipital lobe. The rest of the nervous system appeared normal, and the remaining viscera showed no metastases or other noteworthy lesion. Microscopically, the tumour was a poorly differentiated oat-cell carcinoma. The nervous system was investigated in the same way as in Case 1,

and no lesion could be demonstrated in the brain, spinal cord, or peripheral nerves. Three days elapsed between death and post-mortem, and histological specimens were not very satisfactory, but good Weigert-Pal preparations were obtained, and it is reasonably certain that no extensive lesion was present. Presumably, therefore, the original lesion was completely reversible, and if so it was almost certainly a demyelinization similar to that of Case 1.

Summary of Case 2. A man of 66 developed a moderately severe peripheral neuritis which, after a rapid onset, improved irregularly for a period of six months, when an oat-cell carcinoma of the left upper lobe bronchus was discovered. Radiotherapy improved the chest condition, but he died six months later of cerebral metastases. The neuropathy, which continued irregularly during treatment, was slight at death, and at post-mortem no lesion (except the metastases, which were clearly a late event) was demonstrated in brain, cord, or peripheral nerves.

Case 3

(Cases 3–5 were found by search of the hospital records, and had not been specially investigated.)

An unmarried civil servant of 51 years had been feeling perfectly well until two months before admission, when he noticed a gradual onset of weakness of his legs. It was not severe, but they felt tired when he was walking. In three weeks they had almost recovered, but he then felt a dull aching pain across his shoulders, and his arms became weak. This weakness gradually increased, until two weeks before admission he took to bed. One week later, his voice became hoarse. There was no paraesthesia or sensory disturbance. He had no cough, and had lost no weight. Apart from an attack of jaundice 30 years before, he had always been healthy. His diet had been adequate; he had been exposed to no toxic hazards, took very little alcohol, and did not smoke. There was no known family history of cancer or of nervous disorder.

On examination, he was an alert, well-built man, who spoke in a hoarse whisper. There was no obvious abnormality of heart, lungs, or abdomen. The blood-pressure was 145/80. His soft palate was weak; the laryngologist reported that the vocal cords moved, but that there was some lack of tension. There was weakness of both arms, and the triceps-jerks could not be obtained. The abdominal reflexes were absent. Power in the legs was generally reduced. The knee- and ankle-jerks could be obtained with reinforcement. The plantar responses were flexor. There was no demonstrable sensory loss. The cerebrospinal fluid was normal in all respects, including the Wassermann reaction, but in the blood this reaction was positive. The blood count showed a slight hypochromic anaemia, but was otherwise normal. Chest X-ray revealed a round opacity 3 inches in diameter, lying in the left lower lobe. One week after admission, he began to deteriorate rapidly. He had great difficulty in swallowing solids, and fluids regurgitated through his nose. His peripheral weakness became extreme; he was unable to sit up alone, and lost all his tendon-reflexes. But he still had practically no sensory loss. He died suddenly five days later.

Autopsy. The lower lobe of the left lung was almost filled by a large tumour arising from the main bronchus, and there was consolidation of the remainder of the lobe. The lower and middle lobes of the right lung showed marked fusiform bronchiectasis. The aorta showed some intimal wrinkling and pearly thickening, but no dilatation. Other organs, including the brain, showed no significant lesions. No metastases were seen anywhere. Microscopically, the

tumour was an oat-cell carcinoma of uniform structure, with extensive necrosis. Syphilitic mesoaortitis was present, but mild in degree and quite inactive. Examination of the nervous system was limited to a block of the basal ganglia and another of the medulla just below the olives: no lesion was found at either site. No peripheral nerves were examined.

Summary of Case 3. A man of 51 was admitted with a motor peripheral neuritis of two months' duration, involving all limbs, palate, and larynx. A silent carcinoma (oat-cell) of the left lower lobe was diagnosed radiologically. The neuritis advanced rapidly, and death occurred within a week. Examination of the nervous system at post-mortem was limited to the brain, and was negative.

Case 4

A married man of 52 years, whose occupation was that of costermonger, had been feeling perfectly well until about one year before admission, when he found that his legs were getting weak. The weakness was not associated with any sensory symptoms. His arms and bladder were not affected. The weakness progressed till he was unable to walk, and then it gradually improved again. He was away from work for about five weeks. Six months later, he began to have an unproductive cough, lose weight, and feel generally unwell. These symptoms progressed until he was admitted to hospital.

On examination, he was a pale, slightly cyanosed, very ill man. There were signs of consolidation in the middle zone of his right lung. The central nervous system appeared normal, except for a little symmetrical wasting of the small muscles of his hands, and a more severe wasting of his legs, with corresponding weakness, and diminished vibration sense below the pelvis. Chest X-ray and bronchoscopy confirmed the presence of a large bronchial carcinoma of the right lung. The blood Wassermann reaction was negative. The cerebrospinal fluid was not examined. A blood count showed a mild hypochromic anaemia. The course was progressively downhill, and death occurred two months later from a haemoptysis.

Autopsy. The right lung contained a nodule of tumour 30 mm. in diameter, arising from the wall of the main bronchus near to, and occluding, the mouth of the bronchus to the middle lobe. Secondary changes included patchy fibrosis of the upper lobe, consolidation of the lower lobe, and gangrene of the middle lobe. A large haemorrhage had occurred into the gangrenous lobe, and fresh blood filled the air passages. The left lung showed emphysema only. The aorta was dilated in its first part, reaching a diameter of 75 mm. immediately above the aortic valve, though the valve itself was normal. Intimal changes of a syphilitic type were present in all parts of the aorta. The other viscera showed no significant lesions. The brain was not examined, permission for this having been refused, but the spinal cord was removed and appeared normal. No tumour metastases were seen anywhere in the body. Microscopically, the tumour was a squamous carcinoma, poorly differentiated in some areas, but in others producing large masses of keratin which had excited a remarkable 'foreign body' giant-cell reaction. Gangrene of the middle lobe was probably due to the tumour invading branches of the pulmonary artery. The aortic lesion showed a few foci of adventitial lymphocytic infiltration and a moderate degree of medial destruction; it was syphilitic in type, but almost completely inactive. Using ordinary formalin-fixed material, sections of the cord were made at three levels, and appeared normal. Weigert-Pal-stained material was unfortunately lost, but

Loyez and Sudan-black stains showed no demyelinization. No peripheral nerves were examined.

Summary of Case 4. A man of 52 had an attack of peripheral neuritis, chiefly motor, and chiefly affecting the legs, from which he appeared to recover, though its residua remained obvious. Six months later chest symptoms appeared, and on admission after another six months a squamous carcinoma of the right main bronchus was found. The neuritis remained stationary, and death occurred two months later from haemoptysis. Post-mortem examination of the nervous system was limited to the spinal cord, which was normal.

Case 5

For many years this 66-year-old man had suffered from a cough, with production of much sputum. Four years before admission he had been pensioned from his occupation as a stoker, which he had held for 20 years. The diagnosis given at that time was hypertension, bronchitis, and emphysema. Nevertheless, he remained in comparatively good health until one year before admission, when he coughed up a little blood. Six months later he began to lose weight and to feel generally unwell. Six weeks before admission he noticed that he had difficulty in swallowing solid food and, unless he was careful, fluids returned through his nose. A week later he felt unsteady, his legs began to feel heavy, and he had difficulty in walking. These symptoms progressed until he was unable to stand. Two weeks before admission his arms and hands became weak, and his speech changed. Eventually, he was unable even to sit up in bed without help. At no time did he have numbness, pain, or paraesthesia. He thought that he had lost about seven pounds in weight. Apart from his chronic cough, he had previously had no severe illness. He came of a healthy family; his father and mother died at the ages of 79 and 88 respectively. He took no alcohol, and his diet, until he had difficulty with swallowing, had always been adequate. He had been exposed to no toxic hazards.

On examination, he was a thin, slightly cyanosed man with an expressionless face and bilateral ptosis. He had moderate clubbing of the fingers. He had no pyrexia. Examination of his chest revealed the signs of fluid at the left base, and a mass in the apex of the left lower lobe. This was confirmed by X-ray. He had auricular fibrillation, and his blood-pressure was 170/120. The central nervous system showed the signs of a severe polyneuritis of a predominantly motor type. The pupils reacted sluggishly to light and accommodation. External ocular movements were poor in all directions; the face was weak, the palate did not move, and there was dysphagia. Sensation on the face was normal. The arms and legs generally were weak. He was unable to sit up by himself. All the tendon-reflexes were absent, even with reinforcement. The plantar responses were flexor. Vibration sense was diminished in the arms, and absent in the legs. There was a minimal sensory loss to touch and pinprick of the 'glove' and 'stocking' type. The abdominal reflexes were all present. The cerebrospinal fluid was normal in all respects. Blood counts showed a polymorphonuclear leucocytosis, but were otherwise normal. The polyneuritis began to improve in hospital. In three weeks he was able to sit up unaided, and some tendon-reflexes had returned. The power of his limbs had increased and, except for vibration, the sensory changes had disappeared. A diagnosis was made of a lung abscess, possibly due to a bronchial carcinoma. Bronchoscopy yielded no direct evidence of a neoplasm. A rib was resected, and the abscess drained.

His general condition continued to improve, until 16 days after operation, and five weeks after admission, he died after a haemorrhage through the chest drain.

Autopsy. The main bronchus to the lower lobe of the left lung was occluded by a small hard tumour-mass, which had invaded the wall of the left atrium near the entrance of the corresponding pulmonary vein. A large abscess cavity, which had been drained, occupied most of the left lower lobe. An organizing fibrinous pericarditis was present, and the heart was pulled over to the left. The remaining viscera showed no significant lesion, and no macroscopic metastases were seen. The brain showed moderate senile atrophy, weighing 1,240 gm., and the spinal cord appeared normal. Microscopically, the tumour was a squamous carcinoma, ill-differentiated, producing no keratin, and with a tendency to assume an adenoid arrangement where it invaded alveoli. In the renal cortex a single microscopic metastasis and an equally minute abscess were found. Numerous sections of the brain and cord, with Weigert-Pal preparations of the cord, were made, and apart from mild subpial atrophy of a senile type, the only lesions noted were two tiny polymorph clusters, one in the left thalamus near the internal capsule, and one in the thoracic cord, at the junction of grey and white matter near the lateral horn. These two lesions were sharply localized, not associated with any local nerve-cell change, nor (at least as far as could be ascertained from an adjoining Weigert-Pal-stained block in the case of the cord lesion) with any demyelinization. They were probably terminal embolic lesions, similar to the small abscess seen in the kidney, and unrelated to the neuropathy. Specimens from the femoral and vagus nerves, and from the cords of the brachial plexus, fixed in formalin and prepared by the Marchi method, showed no obvious lesion, but unfortunately no Weigert-Pal fixation was done. Sections of the formalin-fixed nerves were stained with Sudan black, and gave an excellent picture of demyelinization in the femoral nerve and brachial plexus. Unfortunately this may be an artefact; Sudan-black staining of formalin-fixed normal nerves, though it often gives a picture little inferior to the Weigert-Pal method, almost equally often produces an abnormal picture. The finding of a *normal* nerve by this method is apparently reliable, but abnormal findings are unreliable. Sudan black seems to be an adequate stain for any myelin which remains after embedding, and such methods as that of Loyez are probably no better than Sudan black in this respect.

Summary of Case 5. A man of 66, whose relevant chest symptoms had lasted a year, developed a severe peripheral neuritis, predominantly motor, which affected his palate first, and later involved all the limbs and the face. On admission, six weeks later, the signs of an abscess of the left lower lobe were found, and this was drained. Some improvement of the nervous symptoms occurred before death. At post-mortem a squamous carcinoma of the left lower lobe bronchus was found. No relevant lesions were found in the brain or spinal cord.

Discussion of the Cases

We have five patients in whom a carcinoma of the bronchus coexisted with peripheral neuritis. In all five, the peripheral neuritis was the dominant feature of the clinical picture at onset, and in two (Cases 2 and 4) no symptoms directly attributable to the carcinoma appeared until some months later. The peripheral neuritis presents no special clinical features. In Case 1 its pathology has been worked out in some detail, and by exclusion it seems probable that the others

were similar in type: that is to say, they were cases of a true peripheral neuritis, with minimal involvement of the central nervous system, and the lesion of the nerves was a reversible demyelinization. The bronchial carcinoma also presents no special features. Three were squamous, two oat-cell. Four out of five were in the left lung (it is somewhat remarkable that of 11 cases we know of in all, eight have involved the left lung). The degree of secondary change in the lung

TABLE

Cases of Bronchial Carcinoma and Peripheral Neuritis admitted to the Hammersmith Hospital, 1941–8

	Number of cases	*Per cent.*
Total admissions	50,000 (*a*)	..
Carcinoma of bronchus	299 (*b*)	0·6 (of admissions)
Carcinoma of bronchus + peripheral neuritis	5 (*c*)	1·7 (of 299)
Peripheral neuritis	28 (*d*)	0·056 (of admissions)
Peripheral neuritis of obscure origin	17	0·034 (of admissions)
Peripheral neuritis + carcinoma of bronchus	5 (*c*)	29 (of 17)

(*a*) This figure is approximate only, as some records were lost by bombing.
(*b*) A small number of cases, in which the records are inadequate, have been excluded.
(*c*) These are the same five cases.
(*d*) Of these 28 cases, 3 had diabetes, 1 diphtheria, 5 febrile illnesses with changes in the cerebrospinal fluid (probably virus infections—three of them formed a small epidemic among the nursing staff) and 1 pernicious anaemia; in 17 no accepted aetiological factor was present. The 5 cases with bronchial carcinoma are included in this 17.

varied greatly. The most striking feature of the clinical histories, and one for which it is difficult to account, is the complete lack of correlation between the size, or rate of growth, of the tumour, and the progress of the neuropathy. The neuritis may recede while the patient is dying of the tumour (e.g. Case 2), while on the other hand it may relapse shortly after a nearly successful pneumonectomy (Case 1). The attack of (presumptive) peripheral neuritis in Case 1, 12 years before his final illness, was probably a coincidence, but may be an indication of some constitutional tendency to this type of neuropathy, excitable by different stimuli. It is highly unlikely that any bronchial tumour was present so long before; no features of the tumour suggested a pre-existing adenoma. The syphilitic aortitis in Cases 3 and 4 we regard as of no significance. There was no evidence of syphilitic disease of the nervous system in either patient.

Statistics. The relevant figures are presented in the Table. As our case for the presence of any association between the two conditions rests entirely on these figures, they deserve careful consideration. At their face value they seem convincing. If we eliminate 11 cases of peripheral neuritis of known aetiology, the remainder form only 0·03 per cent. of admissions. Among our 299 cases of bronchial carcinoma the expected frequency of peripheral neuritis is then 0·1 of a case. It requires no mathematical analysis to establish five cases as significantly in excess of this. Looked at from the opposite angle, our 17 patients with peripheral neuritis should include 0·6 per cent. suffering from bronchial carcinoma, again 0·1 of a case; in fact, they include five, or 29 per cent. It is

noteworthy that these 17 cases of peripheral neuritis include no other examples of malignant disease; one patient had cirrhosis of the liver, and, two years after the neuropathy had cleared up, developed a hepatoma, but this is not likely to be relevant. The different groups of which the Table is composed have a similar age and sex incidence, and no great inaccuracy can have arisen through disregarding these factors. The only major source of error is in the figure for the general incidence of peripheral neuritis. The five cases of the combined diseases were found by scrutiny of the notes of every case of bronchial carcinoma; the 23 cases of peripheral neuritis without bronchial carcinoma are merely those appearing with that diagnosis in the hospital index. The record is imperfect, a fact which is shown by the presence in the index of only one of the three combined cases which were found by search. The reasons for this imperfection are numerous, and will be familiar to anyone who has attempted to use any reasonably simple hospital index system. So far as we can tell, the real frequency of peripheral neuritis might possibly be as much as three times that shown by the index, but not more. That being so, the expected number of cases of peripheral neuritis, among our 299 of bronchial carcinoma, may rise to 0·3—still a long way from the actual figure of five.

To ensure that we have not been misled by this comparison of dissimilars, we have examined a control series of 600 case notes. In an attempt to gain additional information about the origin of the association, we used 300 cases of carcinoma of sites other than the lung, and 300 cases of chronic lung disease other than carcinoma. Apart from this, the cases were gathered at random by the records department, and examined by us, using the same criteria as we had used in the cases of bronchial carcinoma. No case presented evidence of peripheral neuritis in any way comparable to that of our five cases-in-chief. Absent ankle-jerks, and even absent knee-jerks, were of course occasionally found among the moribund, the senile, and the oedematous, but we were not concerned with such minor disorders; they were, in any case, just as common in our bronchial carcinoma series. The material at this stage seemed to be worth a formal statistical analysis. An event had occurred five times in one sample of 300, and 0 times in another of 600. The probability that this was a mere chance variation in samples of a uniform population may be calculated by the Yates formula for χ^2 in the fourfold table (Hill, 1948). It is considerably less than 0·05. It is necessary, in fact, to reduce the number of cases from five to three before P begins to rise above the traditional 0·05. Our failure to find cases of peripheral neuritis in a random series indicates that our estimate of its general incidence is not much too low, and reinforces our belief that we have provided a strong case for the presence of a real, if small, association between the two conditions.

Valuable confirmation of our findings has come from some unpublished observations of Dr. A. J. Lea. Among 141 proved cases of carcinoma of the lung from the files of the Ministry of Pensions, collected for other purposes, there are three with unexplained peripheral neuritis. This incidence of 2·1 per cent. compares remarkably well with our own of 1·7 per cent.

Basis of the Association

No obvious cause for the association presents itself. The sceptical may choose to suppose that we have failed to find microscopic metastases, and short of serial sections of the entire nervous system one cannot entirely eliminate this possibility; but the multiple systematized reversible lesions, clinically present in all cases, are very difficult to explain by tumour permeation or embolism, and no evidence of any such process was found. Arsenic is the only classical cause of polyneuritis which is also carcinogenic. But there was nothing to suggest arsenic poisoning in any of our cases, and at least in the two recent cases it was very carefully inquired for. Nor is the lung a very probable site of arsenic-induced carcinoma. Tuberculosis has been mentioned as a cause of peripheral neuritis by most text-books since Oppenheim published a case in 1886, but no sign of it was present in any of our cases. It is incidentally conceivable that Oppenheim's case, with its upper lobe cavitation, was one of bronchial carcinoma. Wyburn-Mason suggests that the polyneuritis is produced by 'reflex' from the lungs. He suggests no possible mechanism for this, and the only evidence he adduces for it is the reflex origin of another complication of bronchial carcinoma—osteoarthropathy. But the origin of osteoarthropathy is itself so uncertain that this is a foundation hardly worth building on. In any case, obvious contrasts present themselves between the two conditions. Osteoarthropathy may complicate a great variety of chest conditions in which, if our second control series and general clinical experience are any guide, peripheral neuritis is not found. Osteoarthropathy, in any one case, runs closely parallel to the chest condition, and is often dramatically cured by a pneumonectomy; no such events occur in peripheral neuritis. It is, however, worth noting that the more generalized pseudo-acromegalic osteoarthropathies seem to be associated with bronchial carcinoma more than with other chest conditions (e.g. Fried's four cases of 1943), and the same may be said of gynaecomastia (del Castillo, de la Balze, and Reforzo Membrives, 1944) which may be a related event.

Denny-Brown's suggestion of a metabolic origin is more plausible. He compares the lesions seen in his cases with the effects of tocopherol and pantothenic-acid deficiency in various experimental animals, and suggests that bronchogenic carcinoma acts either by capturing some essential metabolite or by producing a substance of anti-vitamin type. A number of difficulties present themselves.

(*a*) The lack of relation between the size, or rate of growth, of the tumour and the progress of the neuritis make it difficult to imagine the mode of action of a metabolite produced or captured by the tumour.

(*b*) Why should it be especially *bronchial* carcinoma? There seems to be no corresponding association with carcinoma in general. Our control series does not include a sufficient number of any one kind of carcinoma to eliminate the possibility that some other types, apart from the bronchial, may induce peripheral neuritis, but at least it speaks against any general

tendency. If the metabolic effect is peculiar to tumours of the bronchial mucosa, it is odd that histologically they may be of diverse types: both Wyburn-Mason's and our series include both oat-cell and squamous-cell tumours, and Dr. Lea's series includes in addition an adenocarcinoma.

(*c*) The detail of the nervous lesion varies considerably. Denny-Brown's cases both showed a predominantly sensory neuropathy, with the maximum damage in the posterior root ganglia, accompanied by a degeneration of muscle-fibres which he thought to be of independent origin. Our one adequately studied case showed a pure demyelinizing peripheral neuropathy, predominantly motor, with no muscle changes. This variety of lesions does not disprove a metabolic origin, for more than one metabolite may be involved, as (as in the case of thiamine, the lack of which may produce neuritic beri-beri or Wernicke's encephalopathy) circumstances may alter the site of attack of a single agent; but it does complicate the explanation.

Peripheral neuritis is not, of course, the only degenerative nervous disease to be associated with carcinoma. In some forms of cerebellar atrophy (see the reviews by Brouwer and Biemond, 1938, and Brouwer and Schlesinger, 1947) death from associated malignant disease is too common to be a chance finding. The detailed anatomy of these cases varies considerably, and their homogeneity has been doubted with good reason, but loss of Purkinje cells seems to be common to all of them. The associated malignant disease has been most often carcinoma of the ovary (Parker and Kernohan, 1933; Kennard, 1935; Zülch, 1936; Brouwer and Schlesinger, 1947; and one unpublished case of Dr. J. G. Greenfield); but bronchial carcinoma (Greenfield, 1934; and two unpublished cases of Dr. P. M. Daniel), sarcoma of the pelvis (Brouwer, 1919), carcinoma of the breast (Casper, 1929), and carcinoma of the stomach (Garcin, Bertrand and Godet-Guillain, 1939–40) are also implicated. There is here no such close association with bronchial carcinoma as we have postulated for peripheral neuritis, and it is probable that some distinct process is involved. The original reports, where available to us, of these pure cerebellar atrophies, show no evidence of peripheral neuritis, and our patients with peripheral neuritis showed no clinical evidence of cerebellar disease. There is the bare possibility that in Greenfield's (1934) cases we are dealing with an intermediate or mixed form.

We have drifted during the above arguments into the assumption (a probable one) that the bronchial carcinoma is the primary event, and the neuropathy secondary. That a peripheral neuritis could produce in the bronchial mucosa a neoplastic change (or indeed any change at all, unless the respiratory mechanism be involved) seems singularly improbable. The last possible hypothesis, that of an unknown common caus , fails chiefly because of the time relationships. All the known causes of peripheral neuritis act in a matter of weeks, while all the known carcinogens which might affect the bronchus would take years. The only carcinogens which act really rapidly are the viruses of the Shope papilloma type. To assume on this slender basis a transmissible virus (occasionally neurotropic) as the cause of bronchial carcinoma seems to be straining speculation a

little too far. We would prefer to leave consideration of the origin of this association with the belief that there is some link between myelin and the bronchial mucosa, of whose nature we are entirely ignorant, and the discovery of which might yield a great deal of knowledge about both structures.

Summary

1. Among 299 cases of carcinoma of the bronchus admitted to the Hammersmith Hospital in the past eight years, there have been five with peripheral neuritis. It is improbable that this is a chance association.

2. In one case it was established that the nerve lesion was a true peripheral neuritis with demyelinization, predominantly motor, and not involving the brain or spinal cord.

3. No satisfactory explanation of the association has yet been offered.

Acknowledgements

We are indebted to Professor J. H. Dible, Professor J. McMichael, Dr. J. Purdon Martin, Dr. C. V. Harrison, Dr. I. Doniach, and Dr. J. G. Greenfield, for help with many aspects of the cases. Dr. A. J. Lea of the Ministry of Pensions gave us a most valuable pre-view of his own series, and Dr. Greenfield and Dr. P. M. Daniel also gave us some details of their unpublished cases. Miss R. Taylor of the records department found us nearly a thousand case records. The sections we have used are the work of Mr. J. Griffin, and the photomicrographs are by Mr. E. V. Willmott. To all these our thanks are due.

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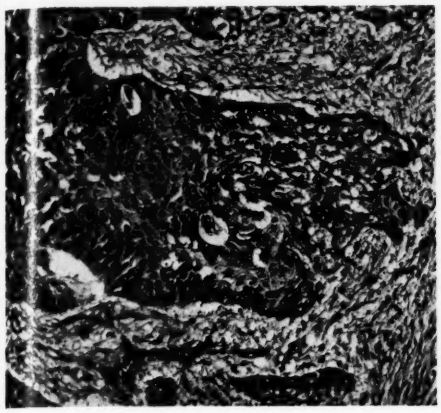

FIG. 1. Case 1. The tumour, from a pleural deposit (haematoxylin and eosin, × 100)

FIG. 2. Case 1. Section of cervical cord; no lesion (Weigert-Pal stain, × 8)

FIG. 3. Case 1. Section of thoracic cord, showing demyelination of a group of nerve-roots (Weigert-Pal stain, × 8). The faintly seen structures near the tip of the posterior horn on the right are vessels, not nerve-roots

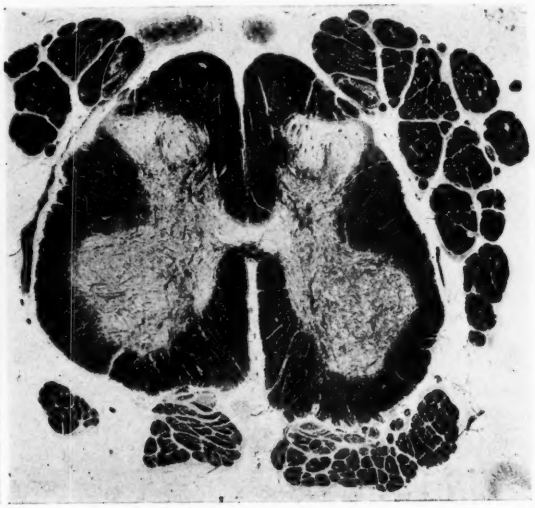

FIG. 4. Case 1. Section of lumbar cord; no lesion (Weigert-Pal stain, × 8)

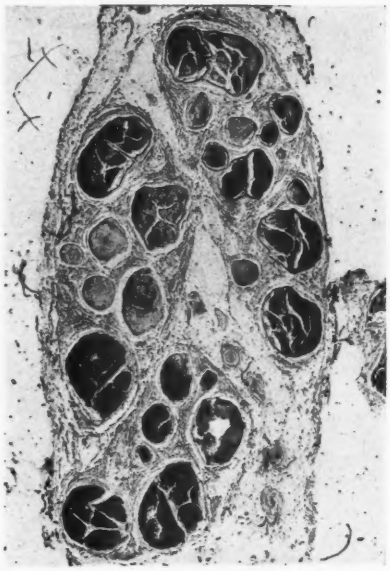

FIG. 5. Case 1. Sciatic nerve, showing extensive demyelinization of many bundles (Weigert-Pal stain, ×6)

FIG. 6. Case 1. Sciatic nerve. A bundle affected with more than average severity (Weigert-Pal stain, ×60)

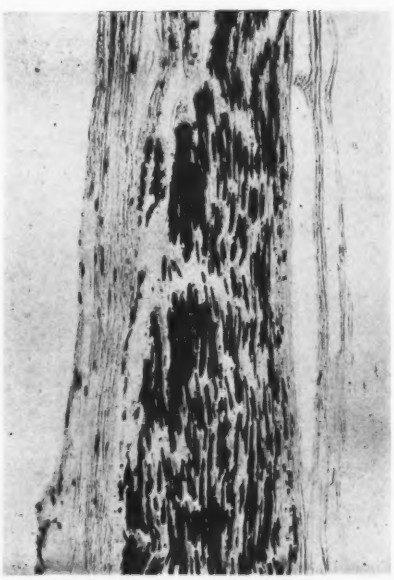

FIG. 7. Case 1. Interdigital nerve of foot, obliquely longitudinal section. Only a few sheaths unstained (Weigert-Pal stain, ×80)

FIG. 8. Case 1. Right phrenic nerve, longitudinal section. Very few intact fibres (Weigert-Pal stain, ×45)

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RESULTS OF TREATMENT OF GASTRIC HYPERACIDITY BY RADIUM, WITH SPECIAL REFERENCE TO DUODENAL ULCERATION[1]

By MURRAY McGEORGE

(From the Department of Medicine, University of Otago and Dunedin Hospital, New Zealand)

Introduction

The importance of hyperchlorhydria as a factor in the causation and continuance of duodenal ulceration is widely recognized. The underlying defect appears to be not only the production of a highly acid gastric juice in response to the stimulus of food, but also the secretion of an abnormally large volume of juice in the intervals between meals, and particularly at night. The various methods of treatment aim at neutralizing or inhibiting this excessive acidity, and success depends largely upon the extent to which this can be accomplished throughout the entire 24 hours. The basis of medical treatment is intermittent neutralization of the gastric juice by the administration of frequent milk feeds, and of antacids, some of which, particularly the colloidal preparations of aluminium and magnesium, have a moderately sustained effect. This treatment does not correct the underlying hypersecretion, and consequently must be continued over long periods to maintain symptomatic relief. Surgical treatment, on the other hand, aims at a more lasting control of the hyperchlorhydria. The operation of gastro-enterostomy was devised, in part, to maintain continuous neutralization through reflux of alkaline duodenal contents, but it was later found that the high output of hydrochloric acid persisted unaltered, with the consequent risk of further ulceration, particularly at the gastro-jejunal site. Partial gastrectomy much reduces gastric acidity, but unless sufficient acid-secreting tissue is removed, secondary ulceration may yet occur, in some cases necessitating further operative measures.

The problem of giving a more prolonged relief of gastric hypersecretion has recently been approached from other angles. Division of the vagus nerves (Dragstedt and Owens, 1943; Dragstedt, Palmer, Schafer, and Hodges, 1944; Dragstedt, 1945; review of 200 papers by Alvarez, 1948) has abolished the response of the gastric mucosa to neurogenic stimuli, without altering the response to histamine, and has had promising clinical results. Somervell (1942–3, 1945–6) described the operation of ligating the small arterial branches running from the main vascular trunks to the stomach wall, the resulting decrease in the blood-supply to the stomach causing a decrease in acidity, both

[1] Received October 4, 1949.

of the fasting juice and of that secreted during digestion. Since the initial reports by Wilms (1916) and Bruegel (1917), the effects of X-ray irradiation of the gastric mucosa have been studied in America, Germany, and Austria, with encouraging, though variable, results. Palmer and Templeton (1939) reviewed the literature, and described in about 100 cases the effects of such radiation directed towards the upper two-thirds of the stomach. In every patient treated there was some reduction in the concentration of the acid, and in the volume of gastric juice secreted. The duration of this reduction was variable: in some cases secretion returned to the initial level in four months' time, while in others marked depression was still present nine to twelve months later. Achlorhydria resistant to histamine occurred in 35 of 88 cases studied, its duration varying from a few days to more than nine months.

Proceeding on the analogy of the depression of ovarian and other glandular activity after irradiation by radium, Jenkins, in 1937, undertook the treatment of a patient with duodenal ulceration by means of radium applied to the gastric mucosa from within the stomach. The radium needles, enclosed in the applicator described below, were swallowed on repeated occasions, for periods of a few hours at a time, the effect meanwhile being studied by serial gruel test meals. From an initial level of 110 per cent. of decinormal HCl, the concentration of free acid fell progressively over a period of six weeks to a minimum level of 40 per cent., after which it gradually rose again. As a result of these observations a more extended trial seemed justified, and in 1942 the results in a series of 14 patients were reported (Jenkins and McGeorge, 1942). Some of these patients have since been re-examined at intervals. The present paper furnishes a full summary of the results obtained in the original 14, and in a further 18 patients subsequently treated along similar lines. The records of 32 cases are thus available for consideration.

Method

The radium applicator. Two 25-mg. needles, or four 10-mg. needles, of radium were secured in the lower end of a rubber tube, 30 inches long. The part containing the radium was enclosed in a rubber bag made of Penrose tubing (Fig. 1). A small hole through the wall of the rubber tube connected it to the bag, which could therefore be distended with water, by means of a syringe applied to the upper end of the tube, after the radium had been swallowed. This arrangement helped to prevent the needles from leaving the stomach, and also held them at least half an inch distant from the stomach wall, an important precaution designed to prevent any intense local radiation.

Method of administration and dosage. Radium treatment was not generally commenced until the patient had completed a full course of medical treatment, including rest in bed. The usual procedure was then to irradiate the stomach for periods of up to six hours per day, until a total dosage of 2,000 to 3,000 mg.hrs. had been administered—that is, seven to ten periods when using 50 mg. of radium, and nine to twelve periods when using 40 mg. The first patients treated received from 2,000 to 2,500 mg.hrs., but the dose was then increased,

and in 21 cases the maximum dose of 3,000 mg.hrs. was employed. A few patients felt nauseated and preferred shorter periods, while in some cases an occasional day off was appreciated. The exact position of the needles was checked from time to time by fluoroscopy. Upon completion of irradiation, the patient maintained for a period his accustomed régime of dietary restrictions and alkalis, and then, if the results were satisfactory, these restrictions were gradually relaxed.

The histamine test. The secretory capacity of the gastric mucosa was assessed before and after treatment by means of the histamine test described by Lander

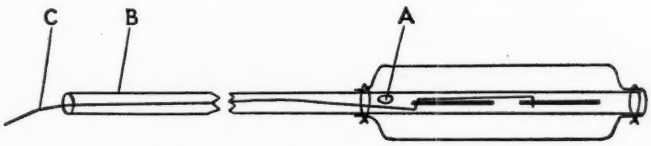

FIG. 1. The radium applicator. A = hole for filling the rubber bag with water after radium has been swallowed. The rubber tube is then clipped at B. C = silk on which radium needles are threaded.

and Maclagan (1934). This test has the following advantages: the procedure is standardized, it provides a maximum stimulus to secretion, and it yields comparatively pure gastric juice suitable for measurement and for chemical analysis. Tests were carried out at 9 a.m. after a 12 hours' fast. A Ryle's tube was passed, the resting juice aspirated, and the stomach then repeatedly washed out with water to remove mucus and to ensure the lodgement of the bulb in the most dependent part of the stomach. One mg. of histamine acid phosphate was given subcutaneously, and more or less continuous aspiration of the stomach contents was then maintained for 50 minutes, the juice being saved at 10-minute intervals in separate bottles. The free acidity of each specimen was then determined, while the rate of secretion per hour was obtained by multiplying by 1·5 the volume of juice collected in the 40-minute period between 10 and 50 minutes after histamine injection. From these figures the rate of secretion of decinormal hydrochloric acid per hour was calculated. In all, 170 histamine tests of gastric secretory function were carried out.

Cases selected for Treatment

With one exception, the 32 patients treated all had a history consistent with duodenal ulceration, and in 27 it was supported by objective evidence of organic disease. All had already undergone medical treatment, some for prolonged periods, and some on several occasions, with subsequent breakdown. In 29 cases the recent symptoms had been of sufficient severity to interfere with working capacity, and to necessitate admission to hospital for further treatment. The demonstration of hyperchlorhydria in these patients suggested the possibility of gastric irradiation as an adjuvant to the standard methods of medical treatment, which had already proved inadequate to maintain symptomatic relief while the patient was at work. In the remaining three cases,

duodenal perforations had already occurred, and in these radium was employed while the patient was free of symptoms in an attempt to reduce the existing hyperacidity, and thereby minimize the likelihood of recurrence. The clinical features of the patients treated may be summarized as follows:

Sex.	All were males.	
Age in years.	20–29	9 cases
	30–39	6 ,,
	40–49	7 ,,
	50–59	8 ,,
	60–69	2 ,,
Duration of symptoms.	Over 10 years	14 ,,
	1–10 years	15 ,,
	Under 1 year	3 ,,
Type of lesion present.		
Evidence of organic lesion		27 cases
Including radiological evidence of duodenal ulcer		21 cases
history of perforation		8 ,,
history of haemorrhage		8 ,,
occult blood in stools		12 ,,
gastro-jejunal ulcer		1 case
No organic lesion demonstrated		5 ,,
Normal X-ray and no complications		4 cases
No X-ray and no complications		1 case.

Histamine Tests prior to Treatment

Four sets of data arising out of the histamine test have been employed as measures of gastric secretory capacity: (*a*) the free acidity of the resting juice, (*b*) the maximum free acidity following histamine stimulation, (*c*) the volume of gastric juice secreted per hour, and (*d*) the volume of decinormal hydrochloric acid secreted per hour. The results of histamine tests prior to treatment have been summarized in Table I, where they are compared with the results from

Table I

Summary of Histamine Tests on Patients prior to Treatment, Compared with Tests on 100 Normal Medical Students

	Mean	*Range*
Resting juice (N/10 HCl %)		
31 radium cases	37	0–79
Maximum free acidity (N/10 HCl %)		
31 radium cases	114	84–143
100 normals	101	0–140
Volume of gastric juice per hour (ml.)		
31 radium cases	343	171–474
100 normals	200	60–340
Volume of N/10 HCl per hour (ml.)		
31 radium cases	348	178–585
100 normals	182	0–340

exactly similar tests carried out on 100 normal medical students by Lander and Maclagan (1934). Attention is drawn to the wide range of values obtained in the control group of young adults, all of whom were entirely free from dyspeptic symptoms. By comparison it will be seen that the group of patients selected for radium treatment showed a tendency towards increased secretion both in maximum acidity and in volume. But a combination of these two measures,

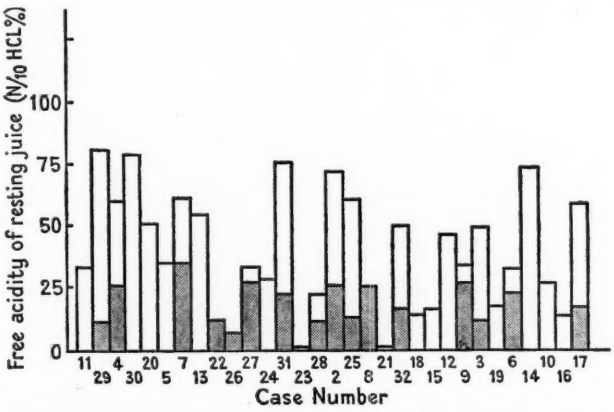

FIG. 2. Free acidity of resting juice, before and after treatment. The total height of the column represents acidity before treatment, the dark section the lowest acidity recorded after treatment.

TABLE II

Acidity of Resting Juice, before and after Treatment
(N/10 HCl per cent.)

Acidity of resting juice	*Number of cases*	
	Before treatment	*After treatment*
0	3	16
1–20	6	11
21–40	9	4
41–60	9	1
61–80	5	..

giving the output of decinormal hydrochloric acid per hour, shows a much wider separation between normal and hyperchlorhydric patients than does either measure by itself. For this reason the histamine test with volume determinations appears to be a more useful measure of gastric secretory function than a simple estimation of acidity following histamine or gruel stimulation.

In one patient only (Case 1) gruel test meals alone were used to assess gastric function.

Results

Patients were recalled at intervals after irradiation for further histamine tests, and for assessment of the symptomatic response. In some cases, where the patient had in the meantime moved from Dunedin, he described his condition by letter after his latest histamine test. Five patients were followed for

periods of between six and nine years, ten between three and six years, nine between one and three years, and eight for less than one year.

1. *Biochemical response.* Depression of gastric secretion occurred in every patient treated except one, but the extent and the duration of this depression

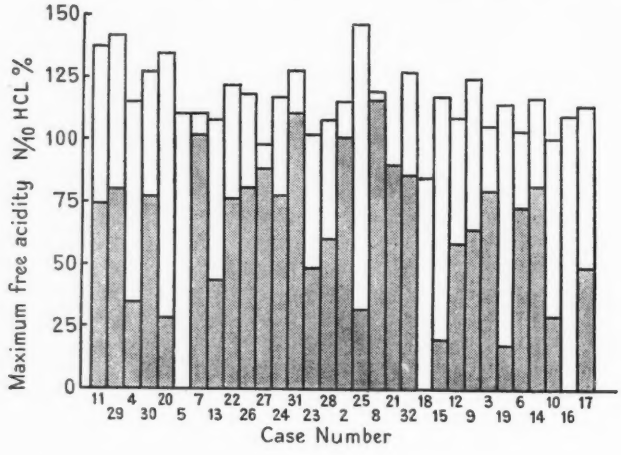

FIG. 3.

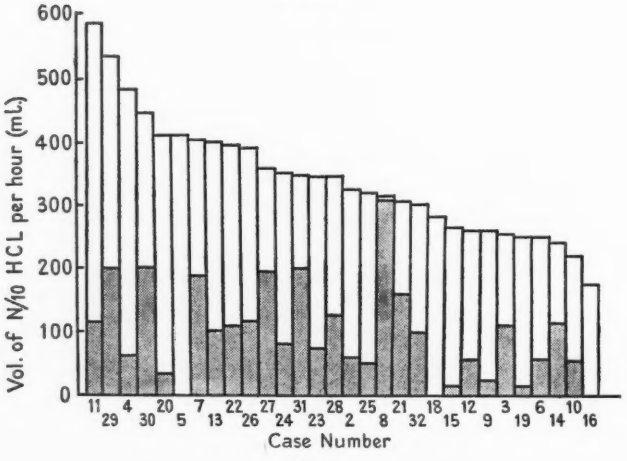

FIG. 4.

FIGS. 3 and 4. Maximum free acidity (Fig. 3) and volume of N/10 HCl per hour (Fig. 4) following histamine stimulation. The total height of the column represents the value before treatment, the dark section the lowest value recorded after treatment.

were variable. The results have been presented mainly in summary, but in addition a few illustrative cases have been set out in detail in an Appendix. (*a*) *Resting juice.* The acidity of the resting juice before treatment, and its lowest acidity observed after treatment, are shown graphically in Fig. 2, and

summarized in Table II. The acidity of the resting juice was diminished after treatment in 28 out of 32 patients, 14 becoming achlorhydric. Of the remaining four patients, two showed no free acid in the resting juice either before or after treatment, while in two there was a higher level after treatment than before. (*b*) *Gastric secretion after histamine.* The general effect of irradiation of the gastric mucosa was to reduce both the volume and the acidity of

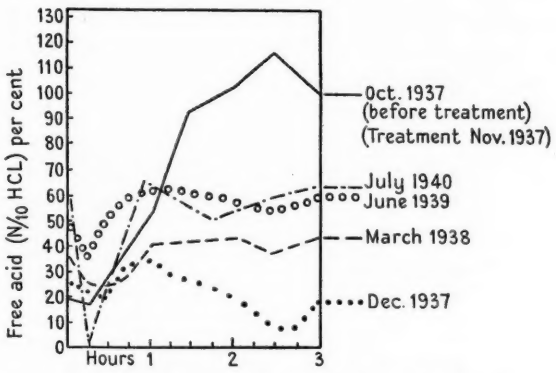

FIG. 5. Free acidity in gruel test meals (Case 1).

TABLE III

Mean Values of Gastric Secretory Function (Histamine Test) before and after Irradiation (31 Cases)

	Before irradiation	*Lowest value after irradiation*
Free acidity of resting juice (N/10 HCl %)	38	9
Maximum free acidity (N/10 HCl %)	114	62
Volume of gastric juice per hr. (ml.)	343	144
Volume of N/10 HCl per hr. (ml.)	348	97

the juice obtained after histamine stimulation, but the response in individual cases showed wide variations. The results in 31 patients are shown in Figs. 3 and 4, where in each patient the figures for free acidity and for hydrochloric acid production before treatment are compared with the corresponding lowest figure obtained after treatment. The free acidity showed some reduction in 28 out of 30 cases. But when the volume of juice is also taken into consideration, a much more definite effect becomes evident: the secretion of free acid per hour was less than 60 per cent. of its initial level in 29 out of 30 patients. In the remaining patient (Case 8) there was no response to irradiation, and no further attempt was made to produce an effect by increasing the dosage. In three cases achlorhydria after histamine resulted. In two cases volume determinations were not made: in Case 1 gruel meals only were employed (Fig. 5), and in Case 17 a previous gastro-enterostomy prevented an estimation. These results are summarized in Table III, in which the mean values of gastric secretory function before irradiation are compared with the lowest corresponding

values obtained after irradiation. It was found that the greatest reduction in gastric acidity was not evident immediately on the completion of treatment, but that some time might elapse before the lowest values were recorded. It was not possible to carry out sufficient tests in the early weeks after radium treatment to obtain full information on this point, but in the few cases in which appropriate tests were made, acidity sometimes continued to fall for periods of a month or more.

Persistence of effects. The data relative to the 18 cases in which biochemical follow-ups were made for periods of at least two years have been further

TABLE IV

Comparison of Initial and Latest Results, in all Cases Re-examined at Intervals for Two Years or Longer after Radium Treatment

				Following histamine stimulation			
		Resting juice (N/10 HCl %)		*Maximum free acidity (N/10 HCl %)*		*Free acid per hour (ml. N/10 HCl)*	
Case	*Time interval (years)*	*Initial*	*Latest*	*Initial*	*Latest*	*Initial*	*Latest*
3	4¾	47	14	106	91	261	249
4	3¾	58	42	114	107	481	189
5	9	30	0	110	18	380	17
8	4¾	0	10	117	117	314	450
11	4¾	34	20	138	104	585	221
12*	2¾	42	2	103	87	265	167
	2	2	0	87	78	167	164
13	5	52	0	107	44	403	92
14	2¼	70	47	117	107	240	231
16	2	16	0	110	12	178	4
18	5¼	14	0	84	39	281	53
20	3	50	40	132	98	415	210
22	2¾	40	20	121	105	394	331
23	4½	0	0	100	73	352	209
25	4½	56	47	143	90	330	238
28	3¾	21	0	108	98	395	275
29	3½	79	44	132	126	533	303
30	2¼	74	70	126	107	442	227
31	2½	74	44	126	116	356	350
Means	3¾	40	21	115	85	356	210

* Two courses of irradiation.

analysed to obtain information regarding the persistence of these effects (Table IV). The free acidity of the resting juice remained appreciably below its initial level in 15 out of 18 patients, including six in whom an induced achlorhydria was still present two to nine years after treatment. Of the remaining three patients, in one the resting juice was achlorhydric both before and after treatment, in one a slight rise was recorded, while in one (Case 30) a transient period of achlorhydria was followed by a return of the acidity, within six months, nearly to its initial high level. Maximum free acidity and free acid production, in response to histamine, also remained appreciably below the corresponding initial level for at least two years in 14 out of 18 patients. In two of these (Cases 13 and 18) the free acid production after five years was respectively 23 and 19 per cent. of the initial level, and had not risen above 36 and 43 per cent. of this

level in any intermediate test, while in one (Case 5) the free acid production after nine years was still exceedingly low. In three patients there was a return, after 24, 26, and 30 months, nearly to the initial level, while in one only (Case 8, in whom there was no response to treatment) did the final figure for acid production exceed the initial one.

Table V summarizes the results of all (not merely the final) follow-up tests, in these 18 patients who were studied for two years or longer. In 14 patients,

TABLE V

Results of Follow-up (Two Years and Over)

(*Duration of follow-up* { *mean* 3¾ years; *range* 2–9 years

Total number of tests . . 81
Mean number of tests per patient 4·3)

	Resting juice (tests)	*Maximum free acidity (tests)*	*Free acid per hour (tests)*
Total number of follow-up tests in which a result was:			
(*a*) *above corresponding initial test* . .	9	0	2
(*b*) *within ±10% of initial test.* . .	14	15	5
(*c*) *below corresponding initial test* . .	58	66	74

TABLE VI

Results of Follow-up (Under Two Years)

	Resting juice (patients)	*Maximum free acidity (patients)*	*Free acid per hour (patients)*
Number of patients in whom final test was:			
(*a*) *higher than initial test* . . .	5	1	1
(*b*) *within ±10% of initial test* . .	..	3	..
(*c*) *lower than initial test*	9	10	11

tests were made for periods of less than two years after treatment, and a summary of the relation of their final to their initial tests is given in Table VI.

2. *Symptomatic response.* In cases of duodenal ulceration, it is not unusual for symptoms to undergo spontaneous remissions of varying duration. There is also a tendency for symptomatic relief to follow the introduction of any fresh line of treatment. For these reasons one must guard against uncritical acceptance of the patient's subjective response to any treatment; indeed, the patient (Case 8) in whom irradiation produced no biochemical changes was free of all symptoms during the next three years. It is difficult and unreliable, therefore, to assess results on a statistical basis. Nevertheless, it does appear that after the use of radium some patients have maintained a freedom from symptoms unknown to them under ordinary medical treatment. In order to bring out any factors which may have influenced the results from the symptomatic point of view patients have been divided into four groups according to their individual assessment of the results. The salient features of each group have then been analysed.

Group 1. Good result, i.e. full work, no symptoms, no dietary restrictions or alkalis. Ten cases.

	Mean	*Range*
Duration of follow-up	4·7 years	1 to 9 years
Duration of symptoms prior to treatment	6 years	7 months to 15 years
Age when treated	36 years	26 to 48 years.

These patients all had symptoms suggestive of duodenal ulceration. In eight out of ten cases an ulcer was demonstrated radiologically, while in one other several episodes of melaena had occurred. Two patients had suffered from perforations, and two from haematemesis. After treatment, they all gradually relaxed their dietary restrictions and alkali medication, and when last seen were completely free of symptoms and were engaged in full work. Only one patient had suffered a slight return of symptoms, necessitating alkali and diet for a few weeks.

Group 2. Significant improvement, i.e. full work, freedom from symptoms, but still some dietary restrictions and/or alkalis. Six cases.

	Mean	*Range*
Duration of follow-up	$3\frac{1}{2}$ years	$1\frac{3}{4}$ to 5 years
Duration of symptoms prior to treatment	16 years	6 months to 40 years
Age when treated	47 years	25 to 68 years.

These patients likewise had symptoms suggestive of duodenal ulceration—in several cases of long duration and considerable severity—which had responded only temporarily or incompletely to diet and alkali. In four an ulcer was demonstrated radiologically, while in the remaining two both a perforation and a haemorrhage had occurred. After treatment, five patients stated that they had remained symptom-free, but preferred to restrict their diet slightly, and to take alkali either intermittently or regularly. The remaining patient still had occasional discomfort if his diet was unrestricted, but this largely disappeared with diet and alkali.

Group 3. Relapse or failure, (A) with subsequent operation, and (B) without subsequent operation. Eleven cases. Further consideration of these cases brings out several points likely to be of value in the future selection of patients suitable for radium treatment.

(A) *Patients requiring subsequent operation* (six cases). All showed X-ray evidence of duodenal ulceration prior to operation.

	Mean	*Range*
Duration of symptoms prior to treatment	16 years	2 to 30 years
Age when treated	49 years	24 to 62 years
Interval between irradiation and subsequent operation	2 years	5 weeks to 7 years.

Case summaries. Case 1. A man aged 62 years had a 20 years' history and a deformed duodenal cap. He was symptom-free for two years after radium;

he then had recurrent pain, haemorrhage, and finally pyloric stenosis. Gastro-enterostomy was performed 6½ years after irradiation.

Case 2. A man aged 50 years, with a 12 years' history and deformed duodenal cap, had had no relief from strict medical treatment prior to radium, and had persistent pain afterwards. Partial gastrectomy, six weeks after irradiation, revealed a chronic duodenal ulcer, penetrating deeply into the pancreas.

Case 12 was a man aged 24 years. He had duodenal perforations in 1938 and 1940, and an initial course of radium in Nov. 1940. In 1942 he had a sudden haematemesis, and in 1943 a recurrence of ulcer symptoms, and a second course of radium was undertaken. He was symptom-free for the next 3½ years; then pain returned for one week, and he had a severe haematemesis. Partial gastrectomy in 1947 revealed a scarred duodenum, and in addition a gastric ulcer, which showed the histological features of a simple chronic ulcer, without evidence of radium reaction.

Case 15 was a man aged 56, with a 23 years' history. Symptoms were still present when radium was used, and no subsequent relief occurred. Partial gastrectomy was done five months later, revealing a healed scarred duodenal ulcer, and an active gastric ulcer. Death occurred from coronary thrombosis three weeks after operation, i.e. six months after radium.

Case 17 was a man aged 57 years in 1943. In 1918 he underwent gastro-enterostomy for duodenal ulcer; in 1924 he had a haemorrhage. In 1940 jejunal ulcer was diagnosed. In 1941 he had a partial gastrectomy, followed in 1943 by severe constant pain, not relieved by strict medical measures. X-ray suggested anastomotic ulcer. Radium therapy was therefore tried, without much expectation of success, but solely in an attempt to avoid a third major operation, which, however, became necessary the following year, when a large anastomotic ulcer was found adherent to, and almost perforating, the transverse colon.

Case 24. A man aged 46 had a three years' history, and a deformed duodenal cap. Pain was still present when radium was used. He enjoyed several months' relief, then had a severe recurrence a year later, following his resumption of bush-felling, with a rough life, rough diet, and alcohol. Partial gastrectomy, 16 months after radium, revealed pre-pyloric and duodenal ulcers.

These six patients were, in general, older than many of those in the preceding groups, and in four of them symptoms had been present for long periods. A most important feature was that in five out of six cases symptoms had failed to respond to preliminary strict medical measures, including rest in bed, and were still present when irradiation was undertaken. In three of these there was no relief of symptoms following irradiation, while in the other three cases remissions lasted for periods of a few months, two years, and three and a half years respectively. Subsequent operation then revealed, in five cases, gross pathological lesions unlikely to respond to any treatment short of radical surgery, while in the sixth the patient subjected himself within a few months of treatment to hard work, unsuitable diet, and alcohol in a bushmen's camp, with an inevitable relapse.

(B) *Relapse, but no subsequent operation.* Five cases.

In one (Case 4), after 10 years' history of duodenal ulceration, the patient joined the army shortly after the completion of radium treatment, and later his symptoms returned. In another (Case 14), a labouring man aged 58 years, with 20 years' history of dyspepsia, radiological examination had shown chronic duodenal ulceration with persistent deformity. The patient's symptoms were not relieved by treatment, but he was able to continue at work. The third (Case 32) was a mental hospital attendant, aged 42 years, with symptoms of epigastric 'boiling and choking', which were not suggestive of duodenal ulceration. The X-ray was normal, and there was no occult blood in the stools. The psychiatrist reported a mildly paranoid personality, with a very considerable functional element. Strict medical treatment resulted in no improvement, and so radium was tried as a last resort. The biochemical result was satisfactory, but symptoms remained unaltered in type and severity. In the remaining two patients (Cases 26 and 28), no particular reason could be assigned for the recurrence of symptoms.

Group 4. Follow-up of under one year. Five cases. These were all free of symptoms when last seen, but the follow-up period (from three to ten months) was too short for the results to be significant.

Pathological Considerations

Five patients underwent partial gastrectomy after irradiation, and in each case the excised stomach was examined histologically. It is of interest to compare these findings with published reports of gastric mucosal changes following X-ray irradiation (Ivy, Orndoff, Jacoby, and Whitlow, 1923 *a*, *b*; Ivy, McCarthy, and Orndoff, 1924; Dawson, 1925; Palmer and Templeton, 1939). Dawson made a detailed study of the microscopic changes in the gastric mucosa of the dog, and noted that the reduction, and eventual disappearance, of acid from the gastric secretion was associated with definite injury to the mucosa, the most striking changes occurring in the superficial portions. He found that the mucous cells were destroyed, and the chief cells underwent cytolysis and lost their granules, while many parietal cells still retained their characteristic form and appearance. Several other observers have also noted that the parietal cells may fail to produce acid secretion even when they present no histological evidence of injury. No infiltrations of white cells were seen in the stomachs examined by Dawson, but plasma-cell foci did occur. The necrotic tissue was apparently sloughed, epithelial regeneration then occurring by proliferation from below. In regenerated mucosa the thickness was markedly reduced, but the structure was histologically normal. Palmer and Templeton (1939) described comparable histological changes in the human stomach following X-ray irradiation. In one patient, in whom death from coronary thrombosis occurred the day after completion of treatment, necrotic changes were present in the superficial parts of the mucosa, with less marked changes and foci of lymphocytes and plasma cells in the deeper parts. In a second case, examined six weeks after irradiation, a widespread gastritis was present, with focal thinning of the mucosa, and both atrophy and hyperplasia of the glands. There was a general

increase in fibrous tissue, with heavy plasma-cell infiltration. The pathological changes observed in the gastric mucosa of our five patients who underwent partial gastrectomy after irradiation by radium have been summarized in Table VII. The commonest change, present in three of the five cases, was the presence of focal collections of lymphocytes and a moderately heavy infiltration by plasma cells. In two there was, in addition, a significant reduction in the

TABLE VII

Pathological Changes in Gastric Mucosa following Irradiation by Radium

			Microscopic appearance				
Case	*Interval between irradiation and operation*	*Macroscopic appearance*	*Lymphocyte and plasma cell infiltration*	*Reduction in parietal cells*	*Superficial necrosis*	*Mucosal atrophy with fibrosis of submucosa*	*Notes*
2	1½ months.	Mucosa smooth	+	−	−	−	Little evidence of radium reaction.
12	3½ years.	Healed gastric ulcer with fibrosis	−	−	−	−	Simple chronic gastric ulcer.
15	5 months.	Flat shallow ulcer	+	+	+	−	Radium reaction.
17	16 months.	Thick gastro-jejunostomy anastomosis	−	−	−	−	Gross inflammatory lesion. No evidence of radium reaction.
24	15 months.	Pre-pyloric ulcer	+	+	+	+	Radium reaction.

number of parietal cells, with a superficial necrosis of the mucosa and occasional mitotic figures. One case only showed atrophic and hyperplastic areas of mucosa with increased fibrosis of the submucosa. Of the remaining two cases, one, examined three and a half years after irradiation, showed a simple chronic gastric ulcer, and the other, 16 months after irradiation, an active gastro-jejunal ulcer with much surrounding inflammatory tissue, but in neither case was there any evidence of a radium reaction.

Complications arising from Treatment

The potential dangers of X-ray radiation of the stomach, which include necrosis of the gastric mucosa, perforation of the stomach wall, regional necrosis of the left lobe of the liver, and necrosis of the ileum, were reviewed by Palmer and Templeton. These workers themselves used an X-ray dosage which was large enough to depress gastric secretion, and in 80 cases so treated recorded one case of localized liver necrosis, one of troublesome diarrhoea, due presumably to intestinal injury, and one of a sudden but not serious drop in the red cell count. No evidence of renal or pancreatic damage was observed. Irradiation of the gastric mucosa by means of intragastric radium has the advantage that the tissue to be treated lies in closer proximity to the source of the rays than does

any other tissue, and it should therefore be possible to grade the dosage so as to obtain the desired therapeutic effect without destruction of neighbouring tissues. The pathological changes in the gastric mucosa already described indicate that some organic changes do occur in this tissue as the result of irradiation, but in the 32 cases treated no evidence was obtained to suggest any damage to neighbouring structures. A certain number of patients complained of nausea while the radium was *in situ*, but some of this discomfort certainly arose from the rubber solution used in making the distensible bag. Repeated blood counts disclosed no evidence of anaemia in any case.

This form of treatment was discussed with our radiotherapy colleague, who pointed out the grave disadvantage arising from the impossibility of estimating, even approximately, the dosage in 'r' units to which the gastric mucosa was subjected. The distensible bag certainly kept the radium at a distance of at least half an inch from the gastric mucosa, and thus avoided any intense local radiation, while the normal movements of the stomach would in addition tend to move the radium about. The dosage employed, estimated in terms of milligram-hours, was determined initially on the biochemical results obtained in the first case of radium treatment (Jenkins, personal communication), in which test-meals were repeated at intervals between short periods of irradiation, spaced over several weeks. Treatment of subsequent patients was undertaken at intervals of several months, in order that results might be observed in each case before further patients were treated.

Discussion

This paper is concerned primarily with the effect of irradiation by radium upon the acid-production of the gastric mucosa, and secondarily with the clinical results following this treatment. It has already been shown in a previous communication that radium does depress gastric acidity, as estimated by the histamine test, but an extension of these observations was desirable, particularly as regards the duration of the effects obtained. In view of the experimental nature of the work the number of patients was limited, but each was observed over as long a period as possible. In selecting cases two general principles were followed. In the first place all patients except one presented a history consistent with duodenal ulceration, with or without complications, and in the majority the usual methods of medical treatment had already proved inadequate to maintain symptomatic relief in association with an active life. Secondly, the gastric acidity of all patients selected ranged from moderate to high levels, no cases of hypochlorhydria being included. Other factors, such as age, length of history, and response to preliminary strict medical treatment, including rest in bed, were subsequently found to be of importance, but were not considered in the selection of these cases.

The biochemical results show that in all cases except one a significant reduction in gastric acidity followed irradiation of the gastric mucosa by radium, and that this reduction generally affected both the resting juice and that

secreted in response to histamine stimulation. The extent and the duration of these effects varied in individual cases. This was possibly due to variations in the amount of radiation received, both from a lack of uniformity of distance between the radium tubes and the mucosa and from a variable position of the tubes relative to the body and the pyloric portion of the stomach. This aspect of the procedure requires further consideration, for, as was realized at the time, it represents an important defect in the accurate control of dosage. The effect of irradiation on the acidity of the resting juice has important clinical implications. Dragstedt and his associates showed that the continuous night secretion in patients with ulcers is greater than in normal individuals. It is unfortunate that determinations of the total night acid-secretion were not made in the present series, but the resting juice obtained in the morning is a sample of the night secretion. Consequently, any reduction in the acidity of the resting juice probably indicates a reduced acid secretion during the night—a point of importance in the healing of ulcers. Although the number of cases followed for two to nine years after irradiation was small, it is noteworthy that acid secretion remained significantly low. A common result was for the period of maximum depression, lasting generally several months, to be followed by a gradual increase both in the volume and in the acidity of the juice, to levels still below their initial value. In only two out of 81 follow-up tests, carried out on 18 patients studied for between two and nine years after irradiation, did the production of free acid after histamine exceed that recorded in the preliminary tests. It thus appears that the effects following radium tend to be more prolonged than those following X-rays, since in the series of cases published by Palmer and Templeton a return to the initial level commonly occurred within a year of treatment. Similarly, Vanzant (1931–2) found that, after bilateral vagotomy in dogs, a marked diminution in gastric secretion lasted for several months, but that later the secretion increased, so that within two or three years it had returned approximately to normal.

The symptomatic response to treatment was much more variable than was the biochemical response, but an analysis of the case-histories shows a correlation between certain clinical features and the subjective response. The clinical features which appeared to have the greatest influence on the result were (1) the age of the patient, (2) the duration of symptoms, and (3) the patient's prior response to strict medical measures, including rest in bed. These factors are not quite unrelated, but are to some extent dependent one upon the other.

1. *The age of the patient.* The patients who responded best to irradiation belonged in general to the younger age-groups.

2. *Duration of symptoms.* Duodenal ulceration commonly commences in young adults, and consequently duration of symptoms is frequently linked with the age of the patient. It appears that a short history in a young patient, irrespective of the severity of symptoms, offers a more favourable chance of success than does a long history in an older patient.

3. *Response to preliminary medical treatment.* The ultimate effect of gastric irradiation is essentially similar to that of the repeated administration of alkali,

i.e. a reduction in acidity. The patient, therefore, who fails to respond to preliminary strict medical treatment, including rest in bed and alkali, is unlikely to respond to radium. This is illustrated graphically in the group of six patients who subsequently came to operation, only one of whom was free of symptoms while on preliminary strict medical treatment. With this exception, operation revealed in each case gross and chronic pathological changes which could not have been expected to respond to more conservative measures. The subsequent history of the psychoneurotic patient who had no evidence of duodenal ulceration, and who failed to respond to preliminary strict medical treatment, also shows that radium cannot be employed as a palliative in cases of gastric discomfort where other methods of treatment have been unsuccessful.

It would appear, therefore, that the following requirements should all be fulfilled before the use of radium is considered: (1) a comparatively young patient, with positive radiological evidence of duodenal ulcer; (2) a reasonably short history, certainly under ten years, and preferably under five; (3) hyperchlorhydria; (4) absence of gross pathological changes, such as extensive scarring, or adherence of an ulcer to neighbouring organs; (5) a satisfactory symptomatic response to preliminary strict medical treatment, including rest in bed, even if this relief only lasts while strict treatment is in progress.

The following lines of investigation are suggested as desirable in any further attempt which may be made to evaluate this procedure: (1) animal experiment, to study the pathological and biochemical changes produced, and the extent and duration of these changes in relation to the amount of irradiation administered, (2) accurate control and estimation of dosage, having regard both to radiation-distance and to the position of the radium needles in the stomach, and (3) an extended clinical trial.

Summary and Conclusions

1. The effect of irradiation of the gastric mucosa, by means of radium placed within the stomach, has been studied in 32 patients with hyperacidity, the majority of whom had duodenal ulceration.

2. The acidity of the resting juice, and also the secretion of free acid following histamine stimulation, were almost always reduced by this means, the reduction in some cases persisting for several years.

3. After irradiation some patients, but not all, experienced symptomatic relief. From an analysis of these cases suggestions are made as to the selection of patients likely to be benefited symptomatically by this treatment.

4. Histological studies were made of the gastric mucosa of five patients, in whom partial gastrectomy was done after irradiation. In three, changes were present indicative of mucosal reaction following irradiation, but in no case was evidence obtained suggestive of damage to neighbouring structures.

5. In cases of symptomatic failure, further treatment along standard lines is not interfered with.

6. In carefully selected patients this method of treatment seems worthy of

further clinical trial, but an investigation of certain technical aspects by means of animal experiment might first be undertaken.

My thanks are due to the physicians and surgeons of the Dunedin Hospital for permission to study patients under their care, to Professor E. F. D'Ath for the histological reports, and to Miss M. N. Woods for the chemical analysis of specimens of gastric juice.

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APPENDIX

Detailed Biochemical Reports from a Few Selected Cases

Case	*Interval following irradiation (months)*	*Resting juice (N/10 HCl %)*	*Maximum free acidity (N/10 HCl %)*	*Volume of juice per hour (ml.)*	*Free acid per hour (ml. N/10 HCl)*
5	Initial	24	108	396	354
		36	110	393	408
	1	0	0	226	0
	4	0	61	370	127
	108	0	18	202	17
13	Initial	52	96	435	403
		27	107	353	323
	1	0	65	295	141
	26	0	52	396	146
	60	0	44	234	92
18	Initial	14	84	430	281
	½	4	28	196	31
	3	0	0	95	0
	6	0	35	226	69
	8	0	38	184	38
	16	0	53	222	84
	25	0	58	283	122
	33	0	47	208	81
	64	0	39	167	53

APPENDIX (*continued*)

Case	*Interval following irradiation (months)*	*Resting juice (N/10 HCl %)*	*Maximum free acidity (N/10 HCl %)*	*Volume of juice per hour (ml.)*	*Free acid per hour (ml. N/10 HCl)*
20	Initial	50	132	404	415
	1	0	30	186	32
	6	0	57	264	112
	10	3	67	213	130
	21	0	88	262	211
	30	33	94	325	285
	37	40	98	234	210
25	Initial	56	143	250	330
	2	14	33	147	46
	5	22	94	225	198
	8	25	106	253	257
	10	30	118	283	283
	15	25	110	300	267
	24	30	82	354	246
	28	44	84	166	125
	54	47	90	276	238
29	Initial	79	132	421	533
		69	139	378	500
	1½	28	80	267	195
	5	20	83	465	331
	9	37	99	350	329
	12	57	126	380	467
	16	61	106	284	304
	40	44	126	264	303
30	Initial	65	111	381	344
		74	126	372	442
	1	0	78	280	202
	6	79	96	307	290
	31	70	107	241	227

616.831:612.118.22

THE NEUROLOGICAL SEQUELAE OF Rh SENSITIZATION[1]

By P. R. EVANS and P. E. POLANI[2]

(From the Department of Child Health, Guy's Hospital, London)

History

In 1875 Orth reported the autopsy of a two-day-old girl who had become jaundiced soon after birth. The brain showed yellow colouring, which was particularly intense around the third ventricle, in the basal ganglia, and in the right hippocampus major. Orth considered that the jaundice was not 'resorptive' but 'haematogenous'. In 1904 Schmorl reviewed the post-mortem records of 120 jaundiced babies, and found that in six of them the basal ganglia had shown yellow discoloration. He introduced the term *Kernikterus* to describe the condition. The clinical concept of familial icterus gravis neonatorum is often credited to Pfannenstiel (1908), and in some countries the condition is known as Pfannenstiel disease. His description was, however, preceded by those of Ashby (1884–5), Blomfield (1901), Arkwright (1902), Smith (1902), Auden (1906), Busfield (1906), Duguid (1906), and Beneke (1907). Ashby reported a family of five children, of whom the last three developed early severe jaundice and died in the second week of life. Nervous signs were observed by Arkwright (1902). One of his patients died on the third day, after convulsions, ocular movements, and spasticity had developed. Another member of the same family developed jaundice early; it lasted for two weeks and was followed by anaemia; at one year, a diagnosis of infantile paralysis of both legs was made; at three and a quarter years the child could stand and walk with support, but the knees were very weak. Beneke (1907) described a family in which the fifth pregnancy resulted in the birth of premature twins, who became jaundiced, showed early clonic spasms which were followed by tonic spasms of the limbs and back, and died on the third day. An autopsy was done on one of them and kernicterus was found. The ganglion cells were yellow, but not degenerate. Esch (1908) described a similar case, with death at six days, and degeneration of some ganglion cells. Pitfield's patient showed jaundice, convulsions, and coma at three days, and mental and motor retardation with ataxia at five years (Pitfield, 1912), but the family history was not typical.

In spite of these early accounts, the connexion between icterus gravis and late nervous sequelae was not widely appreciated. Wilson's discovery of hepato-lenticular degeneration directed medical thought into new channels, and Wilson himself (1912) drew attention to 'an analogy of an interesting and instructive kind' between the kernicterus of icterus gravis neonatorum and hepato-lenticular

[1] Received November 15, 1949.

[2] Working with a grant from the National Birthday Trust Fund.

degeneration. The relevance of Guthrie's demonstration of a child with a typical family and personal history of icterus gravis, who at 19 months showed hypotonia and choreo-athetosis, was at once apparent to his audience, and Parkes Weber hailed it as the first clinical description of kernicterus (Guthrie, 1914; Weber, 1914). Since then many other cases have been described. The description by Hart (1925) of pure chorea in a girl of 12 years, who had suffered from prolonged severe neonatal jaundice, is noteworthy. Urechia (1942–3) mentions a similar case which he described in 1926. It is interesting to find that Hart practised exsanguination-transfusion at this early date. Cornelia de Lange (1934) was the first to report a case with neurological abnormalities but without yellow staining of the brain, in a child aged eight months. She also wrote other valuable pathological papers (de Lange, 1934, 1935, 1936; van Westrienen and de Lange, 1937–8).

The cause of the disease remained obscure throughout this time, in spite of de Lange's prescient suggestion of an interaction between foetal agglutinogens and maternal isoagglutinins (de Lange and Arntzenius, 1929). Darrow (1938) suggested the possibility that the mother was sensitized to foetal haemoglobin, the red cells of the foetus being subsequently destroyed by maternal antibodies. In 1939 Levine and Stetson discovered atypical agglutinins in the blood of a mother who had given birth to a stillborn foetus (Levine and Stetson, 1939). In the following year Landsteiner and Wiener (1940) announced the discovery of the Rh blood group, which led to the conclusion (Levine, Katzin, and Burnham, 1941) that icterus gravis neonatorum might be due to immunization of a Rh-negative mother by a Rh-positive foetus. The pathological basis of icterus gravis neonatorum is now clear, but the reasons for the occurrence of kernicterus as a complication still await elucidation.

Selection of Cases

Many paediatric text-books give no precise indication of the nature of the nervous sequelae of kernicterus. Since the longest series hitherto reported in detail is the eight cases of Lande (1948), we have thought it worth while to try to draw a clinical picture from our own 16 patients and from well-authenticated cases reported by others. In order to clarify the picture we have included, among our own cases, only those in which there was a typical familial and personal history of erythroblastosis foetalis, with neurological abnormalities and with Rh sensitization. Cases in which incompatibility of the ABO groups, or septic jaundice, in the absence of Rh sensitization, may have been operative, have been omitted. The cases were seen in 1946–8 by one of us (P. R. E.) in the Children's Out-patient Departments of Guy's Hospital, the Hospital for Sick Children (Great Ormond Street), and the Evelina Hospital for Sick Children. A number were seen at a selection clinic for a Cerebral Palsy School, or privately. Eight of the cases have been referred to, without description, in a paper on cerebral palsy (Evans, 1948).

The diagnosis of Rh sensitization may be made in various ways, some of which are more reliable than others.

1. The diagnosis is virtually certain, (*a*) if there are Rh antibodies in the baby's blood, or if his red corpuscles are shown to be sensitized by the direct Coombs test (Coombs, Mourant, and Race, 1946); or (*b*) if the patient has suffered from icterus gravis neonatorum, the mother's serum contains Rh antibodies, and there has been opportunity for previous sensitization by pregnancies, miscarriages, or transfusions. The assurance that these latter cases are cases of Rh sensitization depends on the observation that all Rh-incompatible children of a mother who has been previously sensitized to the Rh group suffer from haemolytic disease of the newborn (Potter, 1948; Arnold, 1949. For exceptions, see Chown, 1948).

All our own cases fall into group 1. They are comparable with the following cases reported by other authors: Cases 1, 2, 3 of Wiener and Brody (1946 *a*); 1, 2, 3 of Yannet and Lieberman (1946); sibling of Case 2 of Third (1946); Cases 3 of Stiller (1947); 1 of Lande (1948); E. C. and M. H. of Biemond and van Creveld (1937, discussed again by de Bruyne and van Creveld, 1948); 7 of Becker and Vogel (1948); 3 H. of de Bruyne and van Creveld (1948). For analysis we have also included Becker and Vogel's Cases 1, 2, 3, 5, 6, although no neurological abnormalities were noted clinically in these babies, who died in the first week of life. Cases 1 of Ziegler (1949) and 1 and 6 of Third (1946) have been excluded because the patients' ages were not stated. Case S. C. of Docter (1945) has been excluded, because there was severe neonatal asphyxia. The total number of cases from the literature included in this first group is 18.

2. The diagnosis is probably correct if there is a typical clinical history; the probability is slightly increased by the detection of Rh incompatibility between mother and child. The following cases fall into this group: Cases 1, 2, and 4 of Stiller (1947); 2, 3, 4, 5, 6, 8 of Lande (1948); Guthrie's case (1914); Cases 4 of Spiller (1915); 3 of Thorling (1922–3); de Lange's case (1924); sibling of Hart's case (1925); Cases 3 of Zimmerman and Yannet (1933); 3 of FitzGerald, Greenfield, and Kounine (1939); that of Illingworth (1939); Cases 1, 5 of Giuntini (1942), and 1, 2, 3 of Coquet (1944); a total of 22 cases.

3. The diagnosis of kernicterus may be established at autopsy, but in the present state of our knowledge it is not absolutely certain that every case is due to Rh sensitization. A typical history is therefore required in order to make the diagnosis more probable. The following fall into this group: Case VIII, family H, of Ylppö (1918); Cases 2 of Palm (1919); 4 and 6 of Thorling (1922–3); 3, family P, of Hoffmann and Hausmann (1926); 1 of Monahan (1933); 1 of Zimmerman and Yannet (1933); 4 of de Lange (1934); 1, 2 of de Lange (1935); de Lange's case (1936); Cases 1 of van Westrienen and de Lange (1937–8); 2 of FitzGerald, Greenfield, and Kounine (1939); 1 of Sobel and Zucker (1940); 4 of Coquet (1944) and van Bogaert (1947); 2 of Pfältzer (1914–15); 1 of C. Hart (1917); Cases 1 and 2 of Huwer (1928–9); A. W. of Diamond, Blackfan, and Baty (1932); 3 of Hawksley and Lightwood (1934); 3 of Giuntini (1942); B. Mc. of Docter (1945); a total of 23 cases. The following cases were omitted because the clinical history was insufficient or atypical: Cases 1 of Burghard and Schleussing (1933); 2 of Hawksley and Lightwood (1934); 1 of Pasachoff (1935); 1 of

Zimmerman and Yannet (1935); 1 of FitzGerald, Greenfield, and Kounine (1939); 3 of de Lange (1935); 5 of Stiller (1947); Zimmerman's case (1938), and that reported on p. 250 of Potter (1947).

Clinical Findings

A report of our 16 cases is given at the end of this paper, where their serological findings are shown in the Table. Our patients, when first seen, ranged in age between four days and 13 years. When last seen they were from four months to 15 years old. They were, therefore, distributed throughout infancy and childhood. In nine cases we were able to obtain an accurate early history; in the others the early details had been forgotten, or were not sufficiently reliable to be included. Opisthotonos, lethargy, and twitchings, particularly of the face, were mentioned among the early features of the disease. In one case a sighing type of respiration, with periods of apnoea, had appeared at the age of 24 hours. Some degree of mental retardation was apparent in seven, or about half of our cases. In the final picture, involuntary movements were found in 12 patients, and in one other athetoid tension or 'mobile spasm' was present. Of the 12 patients with involuntary movements, athetosis was diagnosed in seven and chorea in five. Signs of pyramidal involvement were present in one of the cases of chorea, and probably in one of the cases of athetosis. Evidence of involuntary movements was therefore present in 13 of the 16 cases. Of the remaining three, Case 2 died at six months of broncho-pneumonia. He showed intermittent opisthotonos and rigidity, particularly of the upper limbs. At post-mortem there was a faint yellow discoloration of the corpora striata and of the dentate nucleus of the cerebellum. Case 3 had fits at three months of age, and at 14 months showed hypotonia and infantile movements, and appeared to be mentally retarded. A lumbar pneumo-encephalogram showed ventricular dilatation. Case 7, at two years and eight months, was a slightly backward and ataxic child. At least five of the 16 patients were deaf.

It may be objected that this grouping is somewhat artificial, and that the cases referred to us in later life were mainly cases of motor disturbance, while cases of mental defect, for example, without motor disturbance, would gravitate to different clinics. While this is a valid remark, it appears that some of the patients show a sequence of neurological events suggesting that the disease follows a pattern, and that different signs and symptoms may be found at different ages. After a usually stormy neonatal period with jaundice, difficulty of feeding, drowsiness, opisthotonos, and respiratory disturbances, there follows a silent period between the ages of one and two or three months. Thereafter rigidity or intermittent opisthotonos, and sometimes involuntary movements, become obvious. In the period between the ages of one and two or three years, hypotonia may be found. This hypotonic phase, during which mistakes in diagnosis are easily made, is probably also transitory, and may be followed by another in which involuntary movements predominate. This is suggested by the observation that in some children (e.g. Case 6) the hypotonia is replaced

by intermittent spasm resembling athetosis. In Case 4 frank hypotonia gave place to involuntary movements. It would be interesting to know what happens to the clinical picture in adult life, as it seems possible that it may undergo further modification. We wish to stress this variability of the clinical picture, a feature which this disease shares with other affections of the basal ganglia, and to which we shall return later. Case 11 is an example. When this patient was first seen at five years, he was a clear example of mild, jerky chorea, the type found as a sequel of kernicterus. When seen three years later, he had a hypertonia preceding, accompanying, and following the involuntary movements, typical of mild athetosis rather than chorea, although a distinction between the two is sometimes difficult (Wilson, 1928) and electromyography fails to show substantial differences (Hoefer and Putnam, 1940; Hoefer, 1942).

When we compare the cases reported by other authors with our own, we find similar evidence of a pattern of signs and symptoms which changes with age. We selected these cases according to the criteria outlined above, the remainder being rejected from the series here analysed. The correspondence is closest in the group in which Rh sensitization was demonstrated, and less close, although still apparent, in the group depending solely on clinical diagnosis. The cases in which the diagnosis of kernicterus was made pathologically serve to fill in the details of the earlier phases, for most of these children died in the first year. From the literature we have taken 63 cases, which with our own 16 gives a total of 79 for scrutiny. Since, however, we are analysing signs and symptoms by their age-incidence, we include examinations of the same child at different ages. Thirty clinical accounts may be used in this way, providing a total of 130 observations on the 79 patients. Examination of the records of patients aged under one month, one to two months, from two to twelve months, one year to two years eleven months, and over three years, should show whether the clinical picture changes as the child grows older.

Under one month. 42 observations:

16 patients with opisthotonos.
11 with muscular spasms, twitchings, fits, or convulsions.
5 with rigidity (but no mention of opisthotonos).
4 with apathy or coma.
2 with slow movements of the limbs.
12 with no neurological abnormality, appearing gravely ill, and dying within a few days. Respiratory difficulty is a bad sign. It was noted nine times.
24 died. Owing to the manner in which cases were selected, this figure, and those in subsequent age groups, do not represent mortality rates for the group.

One to two months. 11 observations:

9 patients without abnormality, although all showed serious neurological signs at a later age.
2 with opisthotonos, in one case certainly appearing *de novo* at six weeks.
1 with slow movements of the limbs.
None died.

Two months to one year. 29 observations:

15 patients with opisthotonos, which, with two exceptions, was not noticed in the neonatal period, or had subsided, to manifest itself again after an interval of at least four weeks.
12 with rigidity or spasticity.
8 with irregular movements.
5 with convulsions.
2 with hypotonia.
10 died.

One year to two years eleven months. 18 observations:

10 patients with irregular movements of various types. One child had athetosis, two choreo-athetosis, and one chorea.
5 with hypotonia, especially of the spinal muscles.
5 with rigidity or spasticity (one case was described as a spastic paraplegia).
8 considered to be mentally retarded.
2 with ataxia.
1 with opisthotonos.
1 with convulsions.
None died.

Over three years. 30 observations:

16 patients with athetosis.
6 with chorea.
3 with choreo-athetosis
} 25 patients with involuntary movements.
10 considered to be mentally defective.
8 with some sort of muscular spasm (rigidity, spasticity, plasticity, &c.).
7 with a positive Babinski sign.
7 deaf.
3 with hypotonia (all aged 3 years only).
3 died.

One of the outstanding early features suggesting neurological involvement in these patients with jaundice is opisthotonos. It is often seen in the first few days of the disease, when convulsions, rigidity, muscular spasms, a cerebral cry, or a bulging fontanelle may be noted. It gradually disappears, and may at this time be an expression of meningeal irritation, or possibly of decerebrate rigidity. This seems unlikely to be the explanation of its resurgence after the age of two months, when it may in fact appear for the first time. In all such cases involuntary movements (chorea or athetosis) eventually supervene, and this opisthotonos (which is often intermittent) may itself be an early form of muscular dystonia. It has also been interpreted as a sort of Parkinsonian rigidity (Giuntini, 1942). Some sort of muscular spasticity is often noted at all ages, but the descriptions do not always allow one to define its nature. It varies from classical spasticity with stretch-reflexes, through plasticity, to muscular spasm in extension, which is especially noticeable on manipulation. Probably different neuromuscular mechanisms are at work. The well-known features of typical spastic paraplegia or spastic diplegia are so uncommon that they cannot be considered as characteristic sequelae of kernicterus. Muscular flaccidity is

not noticeable in the early months, except in moribund patients. Towards the end of the first year it is often seen. It is more obvious in the trunk and neck than in the limbs. It gradually disappears during the ensuing years. Irregular movements may be noted early. Becker and Vogel (1948) described choreoathetosis in the first month, de Bruyne and van Creveld (1948) mowing move-

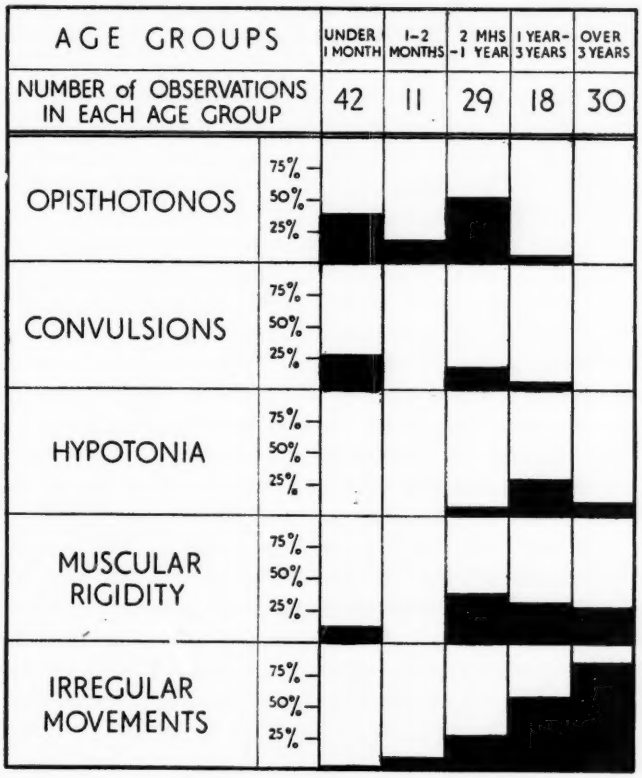


Fig. 1.

ments 'comme le faucheur dans les champs' (de Lange, 1936). Although their incidence increases with age, they are not common in the first year; six patients, who ultimately developed such movements, appeared normal and healthy between the ages of one and three months. After the age of three years, approximately five out of six of the survivors of kernicterus show involuntary movements. These are usually athetoid and associated with spasm. This muscular spasm seems usually to appear before or with the athetosis, and not as the superadded athetoid tension described by Phelps (1941). Chorea has been seen in six of the 30 patients over three years old. The five cases we have personally observed are the only examples of chorea in a series of 114 cases of infantile cerebral palsy, so it seems to be a particular manifestation of kernicterus. It must be noted that the movements may not occur until the child is several

years old. Kernicterus chorea is not precisely similar to Sydenham's chorea, for the movements are more rapid and jerky. Convulsive movements occur in some cases in the neonatal period, and, in a smaller number of patients, can be found throughout the first year. They are rare later. Kernicterus does not generally cause epilepsy. Blindness is recorded in only one of these cases, but deafness is common. It is recorded in approximately 20 per cent. of patients over one year of age. It is sometimes partial, and sometimes appears to be complete.

About three kernicteric patients out of every five die in early life. Of the survivors, it appears that most develop severe, symmetrical muscular in-co-ordination, usually associated with athetosis. The disability is considerable, and the disturbance of function, which may be associated with deafness, renders the accurate assessment of intelligence extremely difficult. In some patients there is little doubt that severe mental defect is present. In many others intelligence is unimpaired. One of our own patients who had chorea (which is less disabling than athetosis) is now doing well at an ordinary school. Another, whose chorea is too severe to allow her to write, can spell and read, attends a school for physically handicapped children, and is said by the teacher to have more than average ability. A third patient with chorea is also of unusual intelligence. Mental defect is almost invariably accompanied by abnormal neurological signs, as in our own patients and in those of Creak (1947). Yannet and Lieberman (1946), in a study of 119 cases of undifferentiated mental defect, found Rh incompatibility between mother and child in a higher proportion than they expected. But in only three of their cases was Rh sensitization proved in addition to incompatibility; in three others there was incompatibility and a significant history, and these six all showed neurological abnormalities as well as mental deficiency. Cappell (1947 *b*) found no unexpected frequency of Rh incompatibility between mother and child in a group of mental defectives.

In Fig. 1 some neurological features of the disease are given in graphic form.

Pathology

In our only patient (Case 2, six and a half months old) whose brain was examined at autopsy, there was yellow staining of the lenticular nucleus, and of the dentate nucleus of the cerebellum. The history indicated that jaundice lasted only four weeks, so that the kernicterus persisted for five and a half months after disappearance of the jaundice. In Becker and Vogel's collected cases, yellow discoloration was always present when the interval after jaundice was not longer than 60 days, and in two cases it persisted for over three months (Becker and Vogel, 1948). The following pathological outline is obtained from an analysis of the autopsy data of those cases from the literature which are considered in the clinical part of our study. The total number of post-mortems among them is 33, and they are from the following sources: Becker and Vogel (1948); Biemond and van Creveld (1937) and de Bruyne and van Creveld (1948); Coquet (1944) and van Bogaert (1947); Diamond, Blackfan, and Baty (1932); Docter (1945); FitzGerald, Greenfield, and Kounine (1939); Giuntini (1942);

Hart (1917); Hawksley and Lightwood (1934); Hoffmann and Hausmann (1926); Huwer (1928–9); de Lange (1934, 1935, and 1936); Monahan (1933); Palm (1919); Pfältzer (1914–15); Sobel and Zucker (1940); Thorling (1922–3); van Westrienen and de Lange (1937–8); Wiener and Brody (1946 *a*); Yannet and Lieberman (1946); Ylppö (1918); Zimmerman and Yannet (1933).

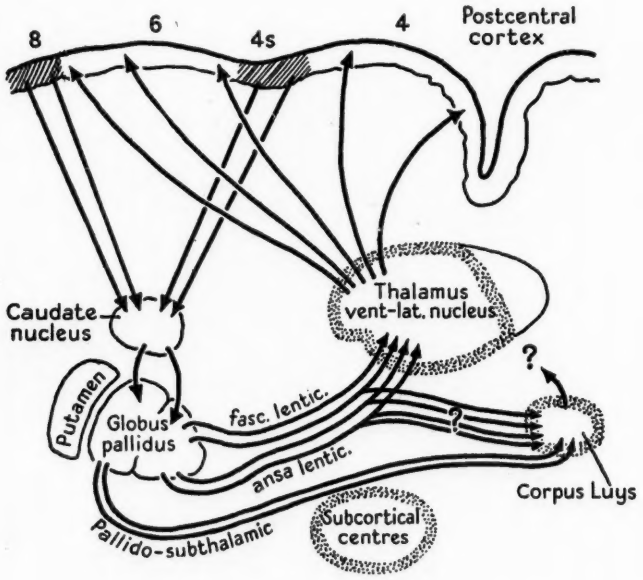
Yellow staining of cerebral substance was seen in 25 out of 26 autopsies of babies under four months of age. Other macroscopic abnormalities (see below) were reported in seven out of 10 children of over three months. Microscopic data are available for all these 10, and for 16 of the 23 infants whose age was less than 16 days. The yellow staining affected, in order of frequency, (1) the corpora striata (20 cases out of 25), (2) the hippocampal regions and the olivary nuclei, (3) next, with equal frequency, the subthalamic body of Luys, the dentate nucleus of the cerebellum, the floor of the fourth ventricle, and localized areas (mainly the flocculi) of the cerebellar surface, (4) the thalamus, various subcortical areas, and various localized cortical regions (hippocampus excepted). Last in frequency came the meninges, the mamillary body, and the anterior and posterior horns of the cord, while the sympathetic and spinal ganglia seemed to escape. These findings agree with the original observations of Clark (Potter, 1947). The other macroscopic anomalies noted in older children include shrinking of the corpora striata (mainly the globus pallidus), marked pallor of the globus pallidus, absence of its normal lamination, and thinning of the fornices. One more interesting macroscopic finding should be mentioned: gross intracranial haemorrhage (subdural, extradural, or subpial) was found in four of the 20 patients who died at less than one week of age. None of the older children showed haemorrhagic lesions. Hawksley and Lightwood (1934) found intracranial haemorrhages in 35 per cent. of their rather older patients. A similar incidence was reported by Leonard and Park (1945). Comparing these figures with the data of Holt (1940), Ford (1926), Sharpe (1923), Roberts (1925), and Clifford (1939), it is difficult to say whether the proportion of intracranial haemorrhages is unduly high in early deaths due to kernicterus. In haemolytic disease of the newborn there is a marked haemorrhagic tendency, which may be responsible for a certain number of fatalities, and which is probably due to hypoprothrombinaemia (Leonard and Park, 1945). It is possible that non-fatal intracranial haemorrhage, in a very few cases of haemolytic disease of the newborn, may cause neurological symptoms in later life. One would expect these cases to show mainly hemiplegias, monoplegias, and asymmetrical and unequal bilateral spastic paralyses (Ford, 1926; McGovern and Yannet, 1947).

Histological changes in the first two weeks of life (16 autopsies) were particularly evident in the globus pallidus, body of Luys and hippocampus. These early cytological changes may be reversible (FitzGerald, Greenfield, and Kounine, 1939; Becker and Vogel, 1948; Biggart, 1949). Perivascular infiltration has been described, but, according to Globus (Becker and Vogel, 1948), it is not abnormal in the newborn. The remaining histological data are of patients aged between three months and six years, and here the picture is more striking. There is a conspicuous loss of ganglion cells, particularly in the centre of the body of

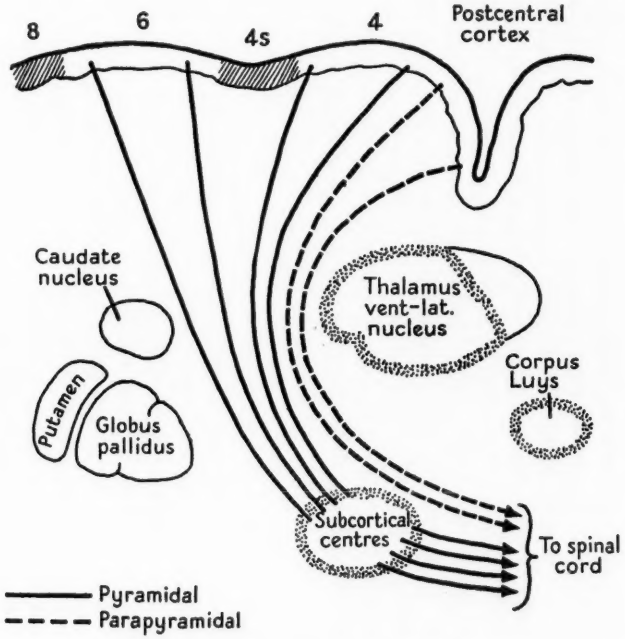
Luys and in the inner segment of the globus pallidus, with gliosis of the affected areas. Demyelinization is frequently mentioned. Cortical alterations are mentioned only twice, and consist mainly in a decrease of cells in layers III and IV. Van Bogaert (1947), in a six-year-old patient, found some histological features suggesting that the degenerative changes were still active. This activity may account for some of the alterations in the clinical picture which occur as the patient grows older; but the main reason probably lies in the developing potentialities of the nervous system of the child, which permit both compensation and imbalance. Wilson (1940) described the temporal variability of clinical syndromes caused by affections of the basal ganglia, and Alexander (1942 *b*) emphasized the delay in appearance of symptoms after injury to these structures. Kennard (1944) demonstrated in monkeys differences in the response to neurological damage at different ages.

Correlation of Pathological and Clinical Findings

The brunt of the attack is borne by the subthalamic body and the globus pallidus. Only once were the changes more severe in the putamen than in the globus pallidus. This distribution of lesions accords with Bucy's and Buchanan's suggestion as to the neurological mechanism of choreo-athetosis (Bucy and Buchanan, 1932; Buchanan, Walker, and Case, 1942; Bucy, 1942 and 1944). Wilson (1928) postulated that a high motor centre, situated in front of the Rolandic area, was responsible for the movements of chorea, and that the activity of this centre was regulated by afferent impulses reaching it via the thalamus from the cerebellum. If these moderating and modifying paths are closed by pathological processes, the activity of the pre-Rolandic centre, in response to other afferent stimuli, becomes unchecked, and choreo-athetosis results, which is 'exteriorized via the corticospinal paths' (Wilson, 1928). In 1932 Bucy and Buchanan confirmed earlier observations which showed that removal of the precentral motor cortex would abolish athetosis. They suggested that this procedure stopped the involuntary movements by abolishing extrapyramidal impulses, and were supported in this view by later experiments with the selective action of barbiturates on cortical area 6, from which the extrapyramidal tracts were supposed to originate. Putnam's success in abolishing the involuntary movements of choreo-athetosis by section of the anterior funiculi of the cord, without damage to the lateral cortico-spinal tracts, confirmed their assumption. Putnam had in fact succeeded in cutting the parapyramidal fibres (Bucy, 1942) which mediate these involuntary movements. Bucy (1942, 1944) views the choreo-athetoid movements as the result of a discharge, via the parapyramidal system (Fig. 2), of impulses which are no longer moderated by the influence of the suppressor circuits described by Dusser de Barenne, McCulloch, and their fellow-workers (Dusser de Barenne and McCulloch, 1939; Verhaart and Kennard, 1939–40; Garol, 1940; Dusser de Barenne, Garol, and McCulloch, 1942; McCulloch, 1944). This suppressor circuit starts in narrow cortical strips (areas 8 and 4*s*) which discharge to the caudate nucleus and thence to the globus pallidus. From here the impulses return by way of



The suppressor circuits



Pyramidal and parapyramidal efferents

FIG. 2.

the thalamus to the precentral cortex, areas 4 and 6 (particularly the latter), from which the parapyramidal system arises and descends into the cord via synapses in subcortical centres. The moderating mechanism should involve also the body of Luys, localized damage to which can cause violent choreiform movements (ballismus) (Martin, 1927; Marcus and Sjögren, 1938; Papez, Bennett, and Cash, 1942; Papez, 1942). In this connexion FitzGerald, Greenfield, and Kounine (1939) wrote 'It is interesting to note that, although maximal destruction of the subthalamic nuclei has been an invariable feature of the cases examined, nothing approaching the syndrome of the corpus Luysi has been observed in them. This may be due to the accompanying involvement of the basal ganglia.'

Incidence of Kernicterus

Nuclear jaundice was found at autopsy in five of 17 cases by Leonard and Park (1945), in 13 of 21 cases by Vaughan (1946), and in 30 per cent. of cases of icterus gravis by Cappell (1947 *a*). Among survivors, permanent damage of the nervous system is less common. An incidence in the region of 10 per cent. is suggested by the figures of Leonard and Park (1945), Vaughan (1946), Cappell (1947 *a*, 1948), Creak (1947), and Diamond (1948). Using the figures of Potter (1948) for estimating the incidence of erythroblastosis foetalis, and those of Diamond (1948) as illustrating the results of the best modern treatment, one may say that out of every 4,000 infants 20 will have erythroblastosis, from which 12 will recover, and one will show permanent neurological abnormalities. The reason why one infant develops kernicterus while others are spared is unknown, but there are peculiarities about its incidence. Kernicterus is rarely or never due to septic jaundice, and never to syphilis or congenital obliteration of the bile-ducts. It is not associated with congenital haemolytic anaemia, but only with icterus gravis neonatorum, which may be due to Rh incompatibility and possibly to ABO incompatibility (see, for example, Yannet and Lieberman, 1948; Ziegler, 1949). Jaundice, and serological reaction between mother and child, appear to be essential for its genesis, yet it is as common in mild as in severe cases, and the spleen is usually smaller in infants with brain damage than in others; from this it has been inferred that there is less haemolysis in the affected children (Vaughan, 1946). Replacement-transfusion increases the chances of survival, but does not diminish the incidence of kernicterus. If more than one child in a family is affected by erythroblastosis, the later children often succumb, but of the survivors apparently 20 to 25 per cent. will show neurological damage (Diamond, 1948; Potter, 1948), instead of the expected 10 per cent. Cappell (1948) in a follow-up of 30 infants transfused within the first 12 hours after birth, found that all developed normally, both physically and mentally. Knowledge of the type or titre of antibody in the blood does not indicate, in the present state of our knowledge, which children will develop kernicterus (Mollison, Mourant, and Race, 1948; Mollison and Cutbush, 1948); nor is it likely to be avoided by the induction of premature labour, for infants of low birth weight are more often affected than bigger babies (Vaughan, 1946).

Some observers contend that the nuclear masses are damaged *in utero*, some that they suffer in the first few days after birth, when the jaundice is most intense. A pathological basis has been sought in the immaturity of the brain at birth and the relative maturity of the basal ganglia (Greenfield, 1947; Blackwood, Dodds, and Sommerville, 1949), in an antigen-antibody reaction between nervous tissue and blood (Vaughan, 1946), and in capillary obstruction by agglutinated blood corpuscles (Wiener and Brody, 1946 *a*, *b*). An asphyxial basis was suggested by Rothman and Hopkins (1943). Docter (1945) favoured an ischaemic theory to explain the localization of brain damage in kernicterus. He mentioned Spielmeyer's work on the vascular susceptibility of the basal ganglia and the hippocampal formations (Spielmeyer, 1930). Zimmerman's conclusions were in accordance with this theory (Zimmerman, 1938). It is supported by the well-known fact that anoxic disease of the brain (e.g. carbon monoxide poisoning) affects the basal ganglia in a striking manner. The peculiarities of the vascular supply to this nuclear region, and to the hippocampus, were studied and confirmed by Alexander (1942 *a*). The pathological mechanism of kernicterus remains obscure in spite of these theories. The clinical picture, on the other hand, is becoming clearer, and is likely to be more familiar in the future as improved methods in the treatment of erythroblastosis foetalis allow more affected children to survive.

Case Reports

Case 1. A boy born at term on June 16, 1946, the second child. The mother's only previous pregnancy had produced a healthy child. There was no abnormality in pregnancy or labour. At birth he weighed 8 lb. 13 oz. At six hours, jaundice and vomiting started, and he was admitted to the Evelina Hospital when four days old. The jaundice lasted 12 days. The spleen was palpable. Two blood transfusions (270 ml.) were given. The lowest haemoglobin estimated was 52 per cent. Opisthotonos was noted on admission, and at three and a half months of age, but it disappeared during sleep. Athetosis was definite at four months, when the child was squinting, and did not smile or fix his eyes on objects. At 11 months he was not sitting up. He died aged 11½ months, following an operation under general anaesthesia for strabismus.

Comment: Prolonged early opisthotonos; early athetosis.

Case 2. A boy born at term on May 19, 1947, the first child. His mother had had a tumour of the breast removed three years previously; the operation was followed by X-ray therapy, and she was given two blood transfusions. There was no abnormality in pregnancy, labour, or delivery. The child's birth weight was 6 lb. 11 oz. Jaundice was present at birth, and was very intense at five days; its duration, and other details of this stage, are unknown. The child was bottle-fed. He was seen at the Evelina Hospital when five and a half months old. He could see and hear, but could not lift his head, and took little notice of his surroundings, but appeared to recognize his mother. He was rather rigid, with the head retracted, but became relaxed in sleep. There was no other abnormality, except that his movements were very jerky. Tonic neck-reflexes were present. One month later the patient was admitted to hospital with broncho-pneumonia, to which he succumbed.

At post-mortem a faint yellowish discoloration of the dentate nucleus of the

cerebellum and of the lenticular nucleus of the cerebrum was noticed. No microscopic examination was made.

Comment: Sensitization of mother by blood transfusion. Head retraction, rigidity, and jerky movements. Death at seven months.

Case 3. A boy born at term on July 14, 1947, the fourth child. There were three previous pregnancies: the first child was healthy, the second was not

TABLE

Results of Serological Tests

	Rhesus (D) Group			*Antibodies*				
				Agglutinating antibodies in mother's serum (saline)	*Incomplete antibodies in mother's serum (albumin)*	*Coombs test*		*Time interval between birth of last affected child and antibody test on mother's serum*
Case	*Patient*	*Mother*	*Father*			*Direct (patient)*	*Indirect (mother)*	
1	+	−	..	+	..	+	..	1 month
2	+	−	..	+	..	..	..	6 months
3	+	−	+	..	+	..	..	10 months
4	+	−	..	..	+	+	..	1 month
5	+	−	+	+	..	+	..	1 day
6	+	−	..	..	..	..	+	1 year
7	..	−	..	+	..	..	..	2 years
8	+	−	..	..	..	..	+	4 years
9	+	−	+	..	..	..	+	4 years
10	+	−	..	..	+	..	..	8 years
11	+	−	..	..	+	..	..	8 years
12	+	−	..	+	..	..	..	9 years
13	+	−	+	..	+	..	+	9 years
14	+	−	..	..	+	..	..	9 years
15	+	−	+	..	+	..	..	13 years
16	+	−	..	..	+	..	..	5½ years

jaundiced but very pale throughout the first year of life, and the third child appeared normal. The fourth pregnancy was normal except for albuminuria. The patient was born with a normal labour and delivery, and weighed 8 lb. He cried a lot, and took feeds with difficulty for the first nine days. At nine days pallor and jaundice were noticed, and the baby was admitted to hospital, where three blood transfusions were given. He remained in hospital for two months, and was discharged to a convalescent home, where three convulsions were recorded and flabbiness was noticed. Usually he lay motionless, with the head turned to the right.

When first seen by us, at nine months old, the patient was markedly hypotonic, with particular weakness of the spinal and posterior neck muscles and of the trapezii and sternomastoidei. All the superficial and deep reflexes were present, the knee-jerks rather brisk. There were no involuntary movements. The cerebrospinal fluid was normal, and its Wassermann reaction negative. Lumbar pneumo-encephalography showed some ventricular dilatation. At 14 months of age he was moving more, but still not attempting to lift his head. The pupils were eccentric, and reacted unequally to light. The optic disks were pale, and blindness and deafness were strongly suspected.

Comment: Hypotonia and weakness at nine and at fourteen months of age; probably deaf and blind.

Case 4. A girl born at term on May 25, 1947. The first two pregnancies produced normal children, the third resulted in a stillbirth at the eighth month.

The fourth pregnancy progressed normally, and ended in the normal delivery of this baby, weighing 7 lb. 1 oz. Jaundice appeared at 24 hours, and progressed, with severe anaemia; it was treated with intramuscular injections of maternal blood, 4–5 ml. each time. At 10 days twitching of the eyes and opisthotonos were noticed. The child was admitted to hospital at 19 days of age, and was immediately given a transfusion of 150 ml. of Rh-negative blood. Anaemia gradually recurred, and at seven weeks another transfusion was given of 70 ml. of Rh-negative blood. Opisthotonos disappeared at five weeks. The child lifted her head at six months old. The teeth erupted at eight and a half months, and were olive-green. When seen at 15 months of age, her motor performance corresponded to that of a baby six to nine months old. No spasticity or involuntary movements were observed, but there was weakness of the muscles of the back. At two years, the child appeared definitely backward, and had continuous jerky movements which ceased only during sleep.

Comment: Jerky chorea and retardation.

Case 5. A boy born at term on November 25, 1946, the third child. The first child was born dead at seven and a half months, after which the mother received a blood transfusion for anaemia. The second was born dead after ante-partum haemorrhage. Rh antibodies were found in the mother's blood during the third pregnancy, and X-rays showed a 'halo' effect; Caesarean section was therefore done in the 37th week. The child at birth weighed 7 lb. 12 oz. Jaundice appeared within 24 hours; anaemia was found and blood transfusion done on the third day. On the eleventh day the child was fretful, refused to suck, and had pyrexia, but the symptoms disappeared overnight with administration of copious fluids. He was seen again at 11 months of age because of myoclonic spasms followed by crying, and was just lifting his head off the pillow, but neither sitting nor talking. He did not take notice of his surroundings, reach for objects, or play with his hands. He could hear loud noises. Adductor spasm was present in the lower limbs. At one year and ten months he recognized people by their voices, moved his arms and legs without fully extending the knees, and would say 'oh dear'. He had frequent short myoclonic fits, with pallor, during which his arms and legs would shoot up in the air. There was limpness of the trunk muscles; the extremities were sometimes limp, but often went into spasm, which at times was symmetrical and at times asymmetrical. This mobile spasm was accompanied by athetoid postures of the hands. The startle-reflex was present. The ocular fundi and tendon-reflexes were normal. There was no fixed adductor spasm, but the hamstring muscles were short.

Comment: Hypotonia, athetosis, myoclonic fits, and probably mental defect.

Case 6. A boy born at term on March 3, 1946, the fourth child. The first pregnancy produced a healthy boy, the second and third two children who died, slightly jaundiced, at the age of one week. The patient received treatment for erythroblastosis in the neo-natal period. He was first seen by us at nine months because he was not holding up his head or using his hands. At 13 months of age there was spasticity of the arms, and if supported he would stand on tiptoe. At 21 months there was hypotonia of the back muscles, and the child was deaf except possibly for high-pitched sounds. At two years, he was still not sitting up, and could regard only objects held level with his eyes. When quiet, the muscles were relaxed; when excited he became very tense. No involuntary athetoid movements were seen. His movements were still infantile in type. At two and a quarter years of age he started to pull himself up.

Comment: Deafness, infantile movements, and intermittent muscular tension resembling that sometimes seen with athetosis.

Case 7. A boy born in September 1944, the second child, the first pregnancy having produced a healthy boy. Pregnancy and labour were normal, but the birth was two weeks premature; the child weighed 6 lb. 10 oz. He developed jaundice on the day of birth, and was admitted to the Hospital for Sick Children, Great Ormond Street, where he was given blood transfusions, and was discharged on the nineteenth day. He sat up at 18 months, started to talk at two and a half years, and walked at two years and seven months. When we saw him at the age of two years and eight months, he walked unsteadily; he put a spoon to his mouth accurately. His words were unrecognizable, and replies slow, but he seemed alert. He had a breath-holding fit on being undressed. There was no spasticity. The psychologist (Miss E. M. Dunsdon) reported that the child was co-operative, that his hearing was normal, proprioceptive sense fairly good in spite of the unsteady balance, and special perception 20 to 25 per cent. below the average for his age; hand and eye showed a left-sided dominance, and the intelligence quotient might be expected to reach 75 to 80.

Comment: Mentally retarded with poor co-ordination.

Case 8. A boy born at term on July 16, 1944, the third child. The two previous pregnancies produced healthy children. The mother had a 'bad heart', and because of this spent the last three months of the third pregnancy in bed. Labour and delivery were normal. The patient was jaundiced within 48 hours, and remained so for 13 weeks. A blood transfusion was given. He talked at two years, and walked at three years of age.

We saw him when four years old, and a history was given of fidgeting, falling over, and grimacing for one year. He appeared underweight. The hand postures were athetoid, but the involuntary movements of trunk, legs, head, and face were choreiform, although more jerky than in Sydenham's chorea. This resemblance to chorea became more noticeable in successive examinations. The child's speech was good, but he was very deaf. The educational psychologist reported an intelligence quotient of 76.

Comment: Onset of jerky chorea at three years; deafness.

Case 9. A girl born on November 20, 1943, the third child. The first child was healthy, the second died, jaundiced, at 36 hours. Pregnancy and labour were normal, the birth two weeks premature, and the birth weight 10 lb. The infant was normal at first, but jaundice was noticed at 24 hours, and she was admitted to the Royal Liverpool Children's Hospital with a diagnosis of icterus gravis. The jaundice lasted four weeks. Two transfusions of Rh-negative blood were given, and she was discharged, apparently well, aged one month. Her age when seen by us was three years and nine months. She could not lift her head from the pillow, but seemed to recognize toys and to understand a good deal. Her teeth were green. There were severe generalized athetoid movements, with a good deal of spasticity of different muscle groups in the limbs.

Comment: Severe generalized athetosis, with some superadded hypertonia of the limbs.

Case 10. A girl born at term on August 21, 1941, the second child. The previous pregnancy produced a healthy Rh-positive boy. A third pregnancy, in 1945, resulted in stillbirth at the eighth month (labour induced); the foetus was jaundiced. The pregnancy which resulted in the birth of our patient was normal. Labour and delivery were normal, and the child's weight 7 lb. 6 oz. Jaundice was present within two hours of birth. At 12 hours there was some respiratory irregularity. Three intramuscular injections of maternal blood were

given. The child talked at 13 months of age, and walked at 18 months. She was seen at the Evelina Hospital at four and a half years, with one year's history of clumsiness, of dropping objects, and of movements of the arms and head. Her central incisors were olive-green. There was a pigmented patch on the back. She showed the typical choreic hand and choreiform movements, with an unsteady gait, and was hypotonic. An X-ray of the bones was normal. Her intelligence was normal. When we last saw her, at the age of eight and a half, the chorea was unchanged. There was never any evidence of rheumatic infection.

Comment: Jerky chorea of moderate severity, beginning in the third year.

Case 11. A boy born at term on April 9, 1941, the third child. The first two pregnancies produced healthy children. A miscarriage preceded the birth of our patient. The pregnancy which resulted in his birth was normal, and ended in a normal labour and delivery. His birth weight was 7 lb. 2 oz. Jaundice appeared at two days, and lasted for four weeks. Stiffness, opisthotonos, and sucking difficulties began on the fifth day and lasted through the first month. He was given an injection of maternal serum. At five months of age there was intermittent opisthotonos. Motor and speech development were delayed. At five years there was hypotonia, his speech was imperfect and explosive, and he had ataxia and a mild jerky chorea. At eight years the movements were more athetoid in type, with hypertonia; speech had improved, and the boy could write in block capitals and read fairly well. His mentality was probably normal. The plantar reflexes were flexor.

Comment: Early opisthotonos; later intermittent opisthotonos. Chorea at five years; mild athetosis at eight years.

Case 12. A boy born at term on June 16, 1940, the third child. The two previous pregnancies produced healthy children. The third pregnancy was normal, and labour easy; the child weighed 7 lb. 12 oz. Jaundice appeared immediately after birth, and lasted for over one week. At first the infant was drowsy, would not suck, and had to be fed by tube for a few days. He sat up some time between the ages of six months and one year, spoke words at between one and two years, and used short sentences at three years. Some deafness was noticed after an obscure illness at five years. When seen by us at six years of age, the patient was very deaf and could hear only shouts. He appeared very nervous and became angry at being examined. There was no alteration in the tendon-reflexes, but the plantar response was probably extensor. No involuntary movements were present. Voluntary movements were exaggerated and athetoid in character. The tone was normal in the arms; possibly there was hypotonia of the legs. Articulation was slurred, but speech understandable. He could write in block capital letters. His intelligence quotient was approximately 50 (West End Hospital for Nervous Diseases).

Comment: Athetosis, mental defect, and deafness; the latter may have been unrelated to the primary disease.

Case 13. A boy born in September 1938, the fifth child. The first child was healthy, then there were three stillbirths before our patient. Pregnancy and labour were normal; he was born one month premature, weighing 5 lb. 9 oz. There were cyanotic attacks and a convulsion at one week, and jaundice began at two days; the child was severely ill and was given an intramuscular injection of father's and mother's blood. Rigidity was noticed at three months. He sat up at three years, walked at seven years, spoke words at two years and

sentences at four. He was nine years old when we saw him, was hearing and seeing well, happy, good tempered, and co-operative. His memory was good, and his school record suggested a mental age of seven or eight years. He had lordosis, weak abdominal muscles, athetoid movements including those of respiration, and slight hypertonia of the calves. The plantar reflexes were flexor. There was an alternating squint.

Comment: Generalized athetosis.

Case 14. A girl born at term on March 11, 1937, the fourth child. The three previous pregnancies produced healthy children. After the birth of the patient, the mother miscarried twice, in the first and third months respectively. The patient's birth weight was 8 lb. 12 oz. Pregnancy, labour, and delivery were normal. Jaundice was present at birth and persisted for two to three months. The patient received three blood transfusions. She sat up at eight months, talked at eight to twelve months, and walked at one year and three months. Abnormal movements were noticed at eight months. She was treated in hospital for rheumatic chorea for two years, from the age of seven and a half. When first seen by us she was 11 years old, and appeared an intelligent girl, with a generalized jerky chorea, without athetosis. Speech and respiration were affected. She could spell and read, but not write. The plantar reflexes were extensor. There was no evidence of rheumatic infection.

Comment: Jerky chorea, with early onset. Extensor plantar reflexes.

Case 15. A boy born at term in August 1933, the fourth child. The first child was normal, the second stillborn, the third stillborn and jaundiced. The pregnancy which produced our patient was normal. Labour and delivery were normal, and the baby weighed 8 lb. He was jaundiced at birth, and this condition persisted for four months. There was great delay of motor development. Irregular movements were noticed towards the eighteenth month, and increased in severity till he was five years old. His mental development was more or less normal, but he was deaf from early infancy. There was severe generalized athetosis.

Comment: Athetosis and deafness.

Case 16. A girl born at term on May 19, 1944, the third child. The previous two pregnancies produced healthy children. Pregnancy and labour were normal, and the child's birth weight was 6 lb. 12 oz. Jaundice appeared on the second day of life. She was admitted to hospital on May 21, and one transfusion of 70 ml. of Rh-negative blood was given. After transfusion the haemoglobin was 85 per cent., and the red cell count 3·3 million per c.mm. She remained an in-patient for one week, and nothing further abnormal was noticed. Jaundice persisted for over 10 days. She sat up at 10 months, stood by herself at two years, and walked at two and a half years of age. At two years she was found to be deaf, and later went to a school for deaf children. When seen at the age of five years, she appeared to be of normal intelligence, and deaf. She was a little hypotonic, and had a rather unsteady and disordinate gait; the latter had been noticed also at school for a few months. She had jerky movements of the head and hands. The appearance was that of a very fidgety child, but the school report said 'balance and control poor', and the mother said 'She can't stand still when you want to tie her bows'. There was no evidence of rheumatic infection. On examination three months later her condition was unchanged.

Comment: Deafness; probably mild chorea of late onset.

Summary

1. Sixteen cases showing neurological sequelae of severe neonatal jaundice, with serological evidence of Rh iso-immunization, are discussed, and the neurological features of the disease are reviewed.

2. The findings in 63 cases selected from the literature are also analysed, and in general found to be in close accordance with our own.

3. The main features of the disease consist of a usually severe neonatal illness with jaundice, opisthotonos, and muscular twitchings. This is followed by a latent period of a few weeks' or months' duration. Later on stiffness or hypotonia, and retardation, may be noticed. Of the older patients, over 80 per cent. show athetosis, chorea, or choreo-athetosis. Mental defect is often, but not always, present. Deafness is frequently found (30 per cent. of our cases).

Acknowledgement

We would like to thank Drs. I. A. B. Cathie, H. Greenburgh, and R. R. Race for doing the serological tests, Dr. B. E. Schlesinger for allowing us to see Case 6, Dr. P. C. Bucy for permitting the use of Fig. 2, and Miss S. Treadgold for the illustrations.

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SENILE PURPURA[1]

By R. N. TATTERSALL and R. SEVILLE

(With Plates 13 to 15)

History

Senile purpura is not rare, and an excellent clinical description of the condition has been available in English for more than a century; in spite of this it has attracted little attention, and is rarely mentioned in current medical literature. In 1836 Bateman, writing in Willans' *Cutaneous Diseases*, described the condition in these words: 'Purpura Senilis, Scurvy of Old Age. I give this appellation to a variety of the complaint of which I have seen a few cases occurring in elderly women. It appears principally along the outside of the forearm in successive dark purple blotches, of an irregular form and various magnitude. Each of these continues for a week to ten or twelve days, when the extravasated blood is absorbed. A constant series of these ecchymoses had appeared in one case during ten years, and in others for a shorter period; but in all, the skin of the arm was left of a brown colour.' Hebra (1868) ignored this clear description, and used the term to include ecchymoses on the legs in association with varicose veins, and this confusion persisted until Unna (1895) revived Bateman's definition and investigated the condition. He described six cases, two in life and four noticed at autopsy. All were aged women, and in all except one the purpura was limited to the extensor surface of the forearm. He noted the naked-eye resemblance between the skin from the forearm and senile facial skin, and described the histological appearances of senile degeneration in the skin from the affected areas. Pasini (1906) made a more extensive study of the condition both clinically and histologically, confirming Unna's histological findings and in addition describing degenerative change in the vessel walls. Jadassohn (1907), under the title of 'purpura factitia senilis', demonstrated the production of the lesions by experimental trauma applied to the extensor surface of the forearm in elderly country-women. Redslob and Bronner (1946) described a case in which senile purpura was associated with intra-ocular haemorrhage, and suggested that the vascular changes described by Pasini might be generalized. In current medical literature the term is used without any explanatory description, and the reader is left with the impression that a diagnosis of senile purpura may only be made by the exclusion of all the other possible causes of purpura in an old person. The present investigation was made in an attempt to clarify the position, and to ascertain the factors concerned in producing this localized form of degenerative change.

[1] Received December 19, 1949.

Observations

Incidence and material. Pasini found 13 cases of senile purpura in 2,325 patients; 957 were over 65 years of age, and it was only in this group that the purpura was seen. His patients comprised eight women and five men, three in the seventh decade, two in the eighth, and eight in the ninth. The 60 cases of purpura dealt with in the present paper were found in the routine examination

TABLE I

Reasons for Admission to Hospital

	Senile purpura (60 patients)	*Whole group (809 patients)*
	%	%
Social reasons	15	10
Senile dementia	30	19
Cerebral thrombosis	17	14
Malignant disease	15	18
Congestive heart failure	11	9
Miscellaneous	12	30

of 809 patients admitted to a geriatric unit for a wide range of medical and social reasons. All were over 60 years of age, and purpura was found with equal frequency in men and in women. It can be seen from Table I that, apart from the rather high incidence of dementia in the purpuric group, these patients represent a fair sample of all those admitted. Fig. 1 shows that the incidence rose with age from 2 per cent. in the seventh decade to 25 per cent. in the tenth decade.

Occupation. Some detail was obtained of the occupations followed by these patients during their working lives (Table II). From this table it is difficult

TABLE II

Chief Occupation

Men		*Women*	
General labourer	27	Domestic work only	23
Quarryman	1	Tailoring	4
Shale oil engineer	1	Textiles	2
Bank clerk	1	Laundry	1

to deduce any aetiological factor common to both sexes, apart from exposure of the forearms to radiation—the men to sunlight at work, and the women to radiant heat in the course of their domestic duties.

Clinical description. A remarkable feature in this variety of purpura is the uniformity of the distribution and appearance of the lesions. These constant characteristics, summarized below, make clinical recognition easy (Plate 13, Figs. 2, 3).

1. In all the patients the lesions were found on the extensor surface and radial border of the forearm, and on the back of the hand, not extending on to the fingers. In three cases there were minimal lesions on the face; on each occasion these were in relation to spectacle frames, and were across the bridge of

the nose or along the side pieces. The purpura was only found in these sites, and not on any other part of the body.

2. The individual lesions were large and irregularly shaped, varying from 1 to 4 cm. in diameter. The colour was a dark purple, and the clear-cut margin contrasted with the ill-defined edge of an ordinary bruise.

3. The skin in the affected areas was inelastic, thin, and pigmented, and in

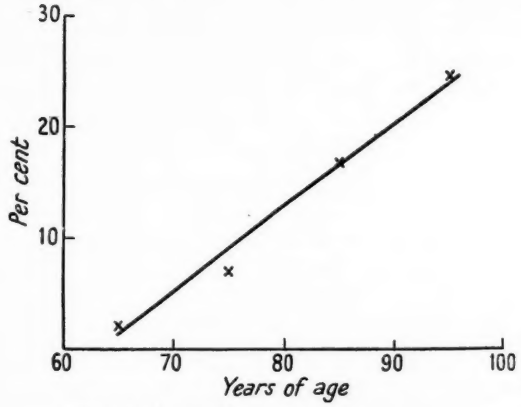

FIG. 1. Age incidence of senile purpura.

many cases showed non-pigmented scars. Permanent freckles were often present, and hair was scanty or absent.

4. The duration of the individual lesions was very variable, some fading in a few days, others lasting many weeks apparently unchanged. The serial

TABLE III

Summary of Blood Tests

	Mean	*Range*
Haemoglobin (%)	83	42 to 120
Red cells (millions)	4·14	1·75 to 6·2
White cells (thousands)	6·8	3·6 to 12·6
Platelets (thousands)	234	142 to 400
Bleeding time	2½ min.	1–4 min.
Clotting time	5 min.	3–8½ min.
Prothrombin time	22 sec.	13–40 sec.
Serum-proteins (%)	5·9	4·2 to 7·3

photographs of a forearm, taken at fortnightly intervals, demonstrate this variability (Plate 13, Fig. 4).

There were no relevant clinical findings in the remainder of the physical examination. Arteriosclerotic changes were present equally in the purpuric and non-purpuric groups of patients; the mean blood-pressure was 194/93 in the former and 179/98 in the latter.

Haematological investigations. The results of routine haematological investigations in 30 patients are summarized in Table III. These results are similar to those obtained from other hospital patients in this age group. Prothrombin

time was estimated by the method of Witts and Hobson (1942) and serum-proteins by the copper sulphate method of Phillips, Van Slyke, Dale, Emerson, Hamilton, and Archibald (1945).

Ascorbic acid excretion tests. The results obtained in purpuric patients, and in a control group of elderly patients, are summarized in Table IV. The method

TABLE IV

Ascorbic Acid Excretion

		Senile purpura 15 patients: mean age 79 years		*Control group* 6 patients: mean age 78 years
		on admission	*after ascorbic acid treatment*	
Excretion (mg. in 5 hours)	*Mean*	104	262	122
	Range	16 to 174	110 to 406	65 to 163

used was to give 1 gm. of ascorbic acid intravenously, and to estimate the urinary excretion over the next five hours (Harris and Ray, 1935). The urinary excretion was very low in both groups of patients, but increased after the administration of ascorbic acid 400 mg. daily for three weeks; this increased excretion was much below the levels obtained in normal young adults, which range from 300 to 600 mg. Plasma ascorbic acid levels (Roe and Kuethen, 1943) were constantly below 1 mg. per 100 ml. on admission, but after the ascorbic acid administration were always above 1 mg. per 100 ml.

Therapeutic tests. These tests were made to see if saturation of the patients with ascorbic acid, rutin, or nicotinic acid would diminish the occurrence of fresh lesions. (1) Ascorbic acid, 300 mg. daily was given for three weeks to 30 patients. (2) Rutin, 150 mg. daily was given for three weeks to 30 patients. (3) Nicotinic acid, 300 mg. daily was given for three weeks to 15 patients. During and after the administrations there was no change in the incidence of fresh lesions.

Capillary fragility. Capillary fragility tests were carried out by the methods described by Göthlin (1937) and Hess (1932). The tests were made on admission, after ascorbic acid, and after rutin administration, and none showed any significant variation from the normal range. In view of the localization of the purpura to the extensor surface of the forearm, comparative readings were made from this area and also from the usual site on the flexor aspect of the forearm; these readings showed close agreement.

Experimental production of the purpura. Most of these patients attributed their purpura to minor injuries resulting from senile clumsiness. The fact that trauma was an important factor in its production was confirmed by applying blunt pressure to the skin in the affected areas. This produced typical purpuric lesions in one to ten minutes, but only on the face and on the extensor surface of the forearm. A similar degree of pressure applied to the skin of the trunk or to the flexor aspect of the forearm did not produce the lesions, and it was not found possible to produce purpura by this method on any area of skin in normal elderly people.

Histology. Specimens of skin were obtained during life, or at autopsy, from 32 patients with senile purpura. In all cases skin was taken from the extensor surface of the forearm or face, and a control specimen from the flexor surface of the forearm or from some other unexposed part of the body. A few specimens were obtained from the same areas of skin in patients of other age-groups, and also from elderly patients without senile purpura. Sections were stained with haematoxylin and eosin or with Lawson's elastic stain. A comparison was made between the staining properties of Lawson's stain and acid orcein; both exhibited the same affinity for elastic tissue, but the contrast obtained with acid orcein was less useful for photographic purposes. The most striking changes were noted in the sections stained for elastic tissue, and the findings in these sections are summarized below on a regional basis.

1. Skin from the dorsum of the hand, extensor surface of the forearm, or face, in patients with senile purpura (Plate 14, Figs. 7, 8; Plate 15, Figs. 11, 12). This skin was noted to be thin and very friable, both at the time of removal and during the preparation of the sections. The epidermis was thinned and the papillae flattened. The fine sub-papillary layer of elastic fibres was normal in appearance. The vessels of the dermis were distended and often tortuous, but their walls were normal in structure, and any elastic fibres present in them exhibited their normal character. The collagen fibres of the dermis were reduced in number and replaced by elastic-staining fibres. These fibres stained less deeply than the normal elastic tissue of the sub-papillary plexus, and were thick, tortuous, and fragmented. In some areas the whole of the dermis was occupied by tangled masses of this abnormal tissue, and the only normal collagen to be seen was round the distended vessels. Sections passing through a purpuric area showed the extravasated red cells lying freely between these fibres (Plate 15, Figs. 11, 12) and there was no evidence of the cellular reaction seen in other forms of purpura. These striking histological changes were found in every case of senile purpura.

2. Skin from the dorsum of the hand, extensor surface of the forearm, or face, in normal patients over 60 years of age (Plate 14, Fig. 6; Plate 15, Fig. 10). This showed the same thinning of the epidermis and dilatation of the superficial vessels. In the dermis there was a general increase in the elastic-staining fibres at the expense of the collagen. These were thicker than usual, but were not tortuous or fragmented, and were distributed normally between the collagen bundles.

3. Skin from the flexor surface of the forearm, or from a covered part of the body, in patients over 60 years, with and without senile purpura. These specimens showed no constant abnormality. In a few cases the elastic tissue showed an increase in amount when compared with a young adult, but it was normal in appearance and distribution.

4. Skin from the extensor surface of the forearm in young adults (Plate 14, Fig. 5; Plate 15, Fig. 9). This showed the normal distribution and character of the elastic and collagen fibres, and is illustrated for comparison with normal and pathological senile skin.

Discussion

The sources of the bleeding. Capillary haemorrhage into the skin normally produces small discrete red or purple areas, varying in size from the barely visible up to areas two to three millimetres in diameter. Haemorrhages of this type were not seen in these patients, except when produced artificially in the performance of a capillary fragility test, and in one man who had both senile purpura and scurvy. This patient, a man of 60 years, had been on an inadequate diet for several years. On admission to hospital, the whole of his body exhibited the typical discrete spots of capillary haemorrhage, and in addition he had on his forearms the large irregular areas of cutaneous bleeding characteristic of senile purpura. On treatment with ascorbic acid the capillary bleeding ceased and capillary fragility reverted to normal, but the senile purpura remained unchanged. When he was seen six months later there had been no recurrence of the scurvy, but fresh lesions of senile purpura were still appearing on the forearms. Capillary fragility tests in the other patients showed no deviation from the normal range; and the shape and size of the lesions in senile purpura are unlike capillary bleeding, even when it occurs into abnormal skin. The difference is illustrated by the case mentioned above. Dilated venules are found, in exposed areas of skin, both in normal elderly people and in those with senile purpura, and these are considered to be the source of the bleeding. Apart from their dilatation, these vessels are normal in histological appearance, and their liability to rupture is possibly related to a change in the support they receive from surrounding tissues.

The production of the lesions. The investigations detailed in Table III do not suggest the presence of any blood dyscrasia in these patients. A deficiency in ascorbic acid excretion, following a standard intravenous injection, was found both in the patients with senile purpura and in other elderly patients (Table IV). There was no history of a deficient diet in any of the patients, and the low ascorbic acid levels in urine and plasma are probably within the normal range for this age group. Apart from the one patient who had scurvy, there was no clinical evidence of a scorbutic tendency, and as the regular administration of ascorbic acid had no effect on the development of fresh lesions, it was considered that there was no connexion between the senile purpura and the low levels of ascorbic acid saturation and excretion. In view of the reported effect of rutin in a variety of haemorrhagic states, it was disappointing that the therapeutic trial of this substance produced no favourable result.

In the early stages of the present investigation it was noticed that a number of patients admitted to hospital for senile dementia also had senile purpura (Table I). Pigmentation of the forearms was also present in these patients, and in order to exclude the possibility that both conditions might be manifestations of pellagra, nicotinic acid was administered; this produced no beneficial effect upon either condition. In a suitable subject it is easy to produce the typical lesions of senile purpura by means of experimental trauma. The lesions can only be produced on those areas of skin in which senile purpura normally occurs,

and in which the characteristic histological changes are found. Further evidence of the traumatic nature of the bleeding is obtained on careful history-taking, when it is usually found that the subjects attribute their purpura to minor injuries. We consider that there is ample evidence that this type of purpura is produced by minor injuries inseparable from normal existence, acting on distended cutaneous venules. Apart from their distension, these vessels have a normal histological appearance, but traverse areas of abnormal connective tissue. The ease with which they rupture may thus be due to lack of the external support supplied by normal connective tissue. It is suggested that the association of senile purpura and dementia has a simple mechanical explanation: the patients are restless, and may injure themselves against the sides of the cot-beds in which they are nursed.

The nature of the histological changes. The normal distribution of elastic fibres in the skin has been studied by Dick (1947), who described the regional variations in the orientation of the fibres, and also the differences in character between the fine branching sub-papillary network and the coarser fibres of the dermis. Ejiri (1936–7) made an extensive study of the changes occurring with age in the exposed skin. He was particularly impressed by a general thinning of the whole skin, a progressive dilatation of the vessels, and an increase of the elastic-staining fibres at the expense of the collagen. Hill and Montgomery (1940) made a similar study of the changes occurring in the skin of the covered parts of the body. They found very slight changes in the elastic tissue, and considered that vascular dilatation, when it occurred, did not increase after the fifth decade. Kissmeyer and With (1922) found evidence of early degeneration in the elastic-staining tissue of exposed skin between the ages of 25 and 40, particularly in fair-haired individuals. In the present series it has not been possible to show a relationship between the severity of the changes and the colour of the hair or type of complexion. Examination of specimens of exposed skin from normal patients of various ages has demonstrated the progressive nature of these changes in the elastic-staining fibres. The more extensive changes which are invariably found in cases of senile purpura appear to be an extreme example of this normal process. Increase in the elastic-staining components of the dermis, in old age, is invariably associated with a loss of the normal elasticity of the skin; Unna thought that both elastic and collagen tissues degenerate, and that the products fuse to form a compound which absorbs elastic stains. Ejiri used a number of staining methods, and was unable to demonstrate this transition; he observed the degeneration, fragmentation, and disappearance of the collagen fibres, and their replacement by an overgrowth of abnormal elastic fibres. Percival, Hannay, and Duthie (1949) considered that the collagen bundles increase in length and undergo a physico-chemical change which makes them absorb the usual elastic stains.

Since examination of the skin by conventional histological methods had failed to explain the loss of elasticity, we submitted specimens of normal and abnormal skin to the Department of Biomolecular Structure, University of Leeds, for further examination by the special technique of X-ray diffraction

photography and electron micrography. The preliminary results of this investigation have been published elsewhere (Reed, Tattersall, and Millard, 1949), and suggest that the essential change in this condition is the presence of degenerate collagen fibres and of much breakdown material. The amorphous breakdown material can be removed by treatment with trypsin, and at the same time the elastic-staining properties of the skin disappear. This suggests that the increase in the elastic-staining components, seen in conventional histological preparations of exposed senile skin, may be a false staining reaction. Gross and Schmitt (1949), working with the electron microscope on normal skin, noted that elastic fibres were rarely seen in the specimens examined, and this finding has been confirmed by Reed (Reed, Tattersall, and Millard, 1949). The main component of the dermis, when examined by the electron microscope, is a palimpsest of collagen fibrils, each bundle of fibrils taking a straight course. These fibrils are inextensible, and it may well be that their intact state and the arrangement described, with its close resemblance to a wire mattress, provide normal skin with its elasticity, and that elastic fibres play a minor role in this function. The degeneration of collagen fibrils in senile skin would then explain the loss of elasticity which is its characteristic feature.

Summary

Senile purpura is a definite clinical entity, first described by Bateman in 1836, which may be recognized by the distribution and shape of the lesions, their natural history, and the age of the patient. The sexes are equally affected, and the condition is unrelated to any systemic disorder or recognizable dietary deficiency.

Histologically, it is constantly associated with an extreme degree of senile degeneration of exposed skin, and the individual lesions are probably produced by minor external trauma acting on inadequately supported skin vessels. Degenerate collagen fibres are found in the affected areas, but it has not been possible to demonstrate any increase in true elastic tissue.

We are indebted to Dr. W. Goldie and the members of his staff, who carried out the pathological investigation and made the histological preparations, and to Mr. J. Hainsworth for the clinical photographs and photo-micrographs. We also wish to thank Professor W. T. Astbury and the staff of the Department of Biomolecular Structure, University of Leeds, for their valuable help and co-operation, and Professor R. E. Tunbridge for his help in preparing this paper.

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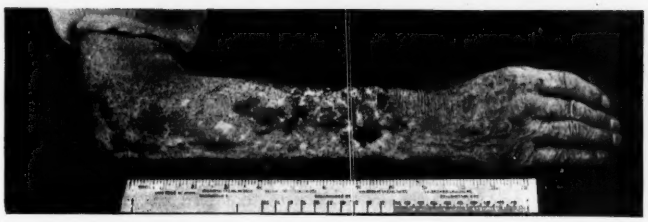

FIG. 2. The typical lesions of senile purpura in a man aged 74. The purpuric areas are large, irregular, and associated with pale atrophic scars

FIG. 3. Similar lesions in a woman of 84. The thin, smooth, and hairless skin is easily seen

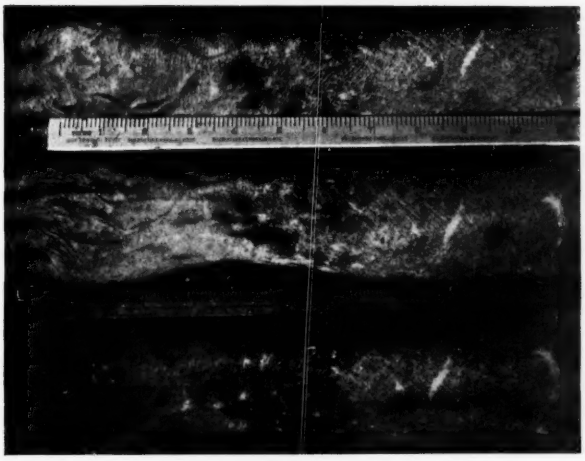

FIG. 4. These photographs of the same forearm were taken at fortnightly intervals, and demonstrate the variable duration of the lesions. Some areas of purpura remain constant for the whole month, while in the middle picture is one area which had not appeared two weeks before and had disappeared two weeks later

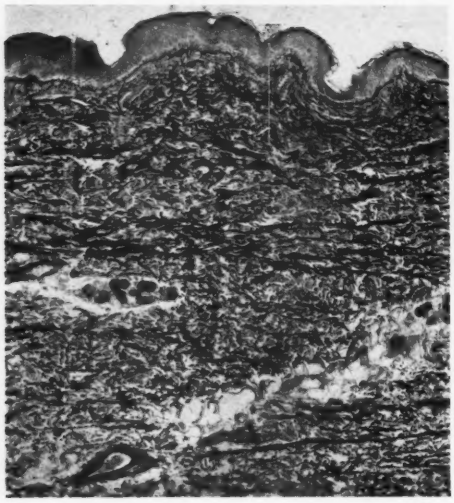

FIG. 5. Skin from the extensor surface of the forearm in a normal adult aged 31. The elastic-staining fibres are in a fine sub-papillary layer and interspersed with the collagen bundles (Lawson's elastic stain, ×45)

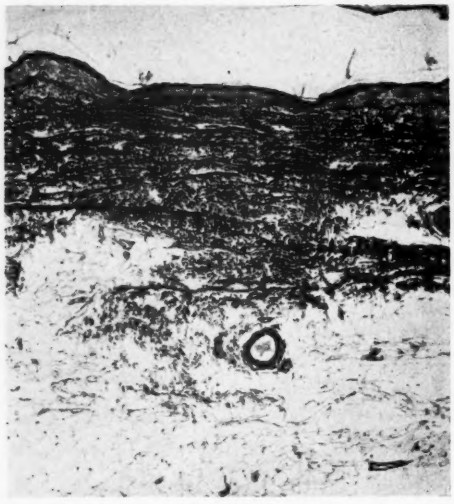

FIG. 6. Skin from the extensor surface of the forearm in a man aged 74. There is a decrease in the amount of collagen, and possibly some increase in the elastic-staining fibres (Lawson's elastic stain, ×45)

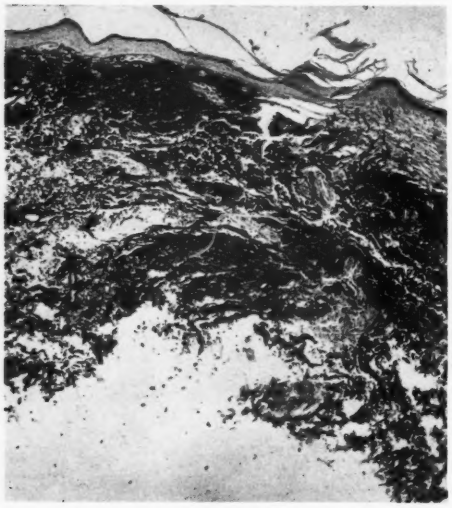

FIG. 7

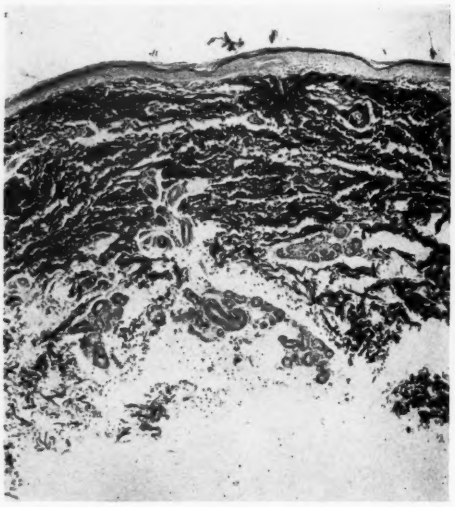

FIG. 8

FIGS. 7 AND 8. Skin from the extensor surface of the forearm in two cases of senile purpura, aged 72 and 83. Compared with figs. 5 and 6, there is an enormous increase in the elastic-staining fibres, and very little normal collagen is to be seen (Lawson's elastic stain, ×45)

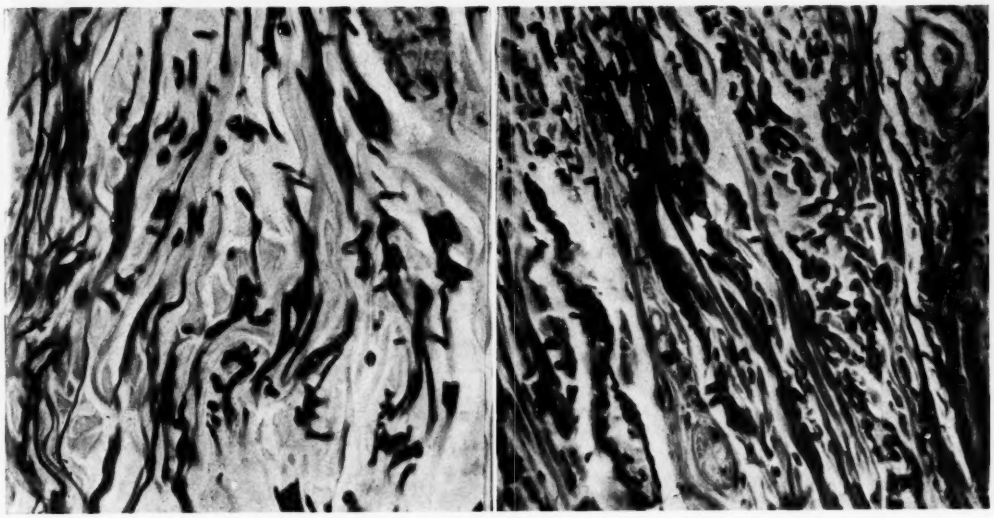

FIG. 9 FIG. 10

FIGS. 9 AND 10. Higher magnification of figs. 5 and 6, showing the normal age variations in the appearance of the elastic-staining fibres (Lawson's elastic stain, ×350)

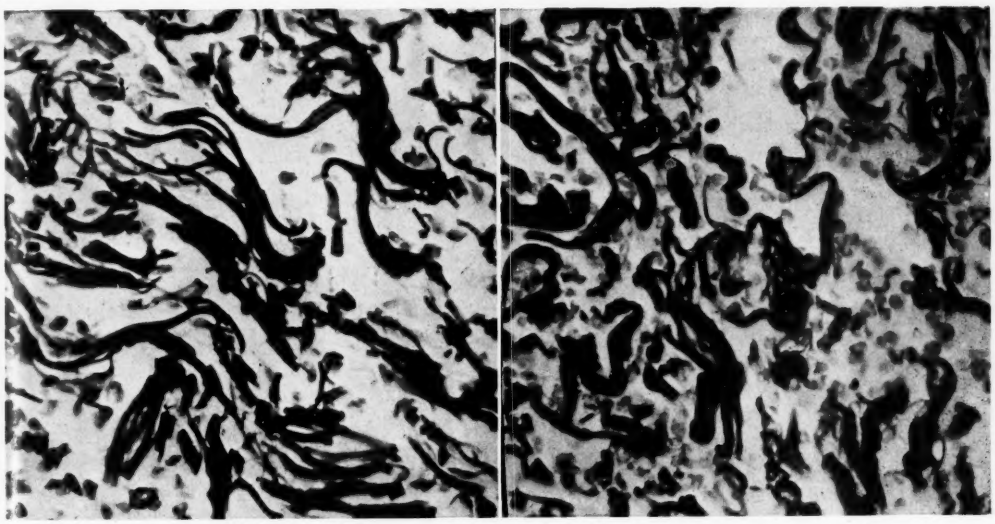

FIG. 11 FIG. 12

FIGS. 11 AND 12. Higher magnification of figs. 7 and 8, showing numerous erythrocytes lying in a loose network of fragmented and tortuous elastic-staining fibres (Lawson's elastic stain, ×350)

616.61–002:616.15

BIOCHEMICAL AND HAEMATOLOGICAL CHANGES IN TYPE 1 AND TYPE 2 NEPHRITIS[1]

By MARGARET H. ROSCOE

(From the Department of Medicine, Manchester University)

Introduction

During the last three years it has been possible to investigate in the Manchester Royal Infirmary 61 cases of nephritis in the active stage of the disease. An attempt has been made to gain a dynamic conception of the biochemical and haematological changes which occur, by studying them serially in each patient during the process of recovery or deterioration. This study has been undertaken for four main reasons. In the first place, no similar study of a considerable number of cases has been published since that of Van Slyke and his fellow workers in 1930. Secondly, since that time Ellis (1942) has introduced a new classification of nephritis. He described two types of the disease, and considered them distinguishable both on clinical and pathological grounds. This conclusion has been confirmed, from the clinical and pathological point of view, by the recent paper of Davson and Platt (1949), but it was desirable to know whether these two main types of nephritis could also be distinguished by specific patterns of disordered physiology. Thirdly, it was hoped to throw some light on the mechanism of oedema formation by a study of the changes, especially in blood-volume, which take place with the occurrence of oedema in the different kinds of nephritis. Finally, since these changes in blood-volume affect the haemoglobin and red-cell levels, the presence of anaemia was recorded and an attempt made to explain its occurrence.

Method of Investigation

The following observations were recorded: the degree of oedema, the presence of blood and albumin in the urine, the blood-pressure, the blood urea and urea clearance. With these we compared the levels of haemoglobin, red cells and cell mass in the blood, and the serum-proteins and cholesterol.

The amount of oedema is difficult to assess, but changes in oedema can be recorded in two ways. The most reliable is by a daily record of weight. At the start of the present investigation this daily record was not possible, and there are always some patients unfit to be weighed. It was often necessary, therefore, to rely on the less satisfactory method of comparing the daily fluid intake with the urinary output. In some cases the fluid balance so found agreed well with the changes in weight, in spite of the fact that the intake of fluid in food, and its loss in perspiration and faeces, were neglected; but in other cases the agreement was poor, probably because of errors in the measurement of urinary output

[1] Received December 31, 1949.

in the wards. Blood in the urine was looked for microscopically, after centrifuging, if it was not obviously present. Albumin was estimated crudely by Esbach's method. Blood-pressure was recorded daily with a mercury manometer, usually by the same person. A diastolic pressure of 90 mm. Hg. or over was considered abnormal, but in the older patients it was sometimes felt that a slight degree of hypertension was unrelated to the nephritis. Haemoglobin was estimated by the alkaline haematin method of Clegg and King (1942), using the artificial standard of Gibson and Harrison (1945) and a selenium-cell colorimeter. Red-cell counts and haematocrit levels were often recorded at the same time. These estimations showed considerable day-to-day variations, which were attributed to alterations in the plasma-volume. This is correct only if no change occurs in the total amount of haemoglobin; but when the time between estimations is short, a change is not likely to have occurred. While such evidence of alterations in plasma-volume is indirect, the method of investigation has the important advantage that serial estimations can be made at short intervals, and the changes in volume followed. Dye methods of direct estimation, on the other hand, cannot be frequently repeated. An accurate objective method of measuring haemoglobin, such as that used here, is very necessary in these circumstances. In one case the indirect evidence of change in plasma-volume was checked by direct estimation with Evan's blue (T 1824). The method used was that of Davis (1942). Two hundred and fifty mg. of the dye were injected intravenously, and its concentration in the plasma was measured after 10 minutes. Although there has been much criticism of the dye method, we feel that the results obtained with it are sufficiently accurate, especially when a comparison is being made at different times in the same patient. The serum-proteins were estimated by the method of Greenberg (1929). Serum-albumin and serum-globulin were estimated in all types of nephritis, but most frequently in Type 2, because the oedema of that condition has been attributed to a low colloid osmotic pressure. Since albumin exerts a much higher osmotic pressure for a given mass than globulin, it is difficult to see at a glance what effect will be produced by a change in both albumin and globulin. Wells, Youmans, and Miller (1933) found, by direct estimation of the colloid osmotic pressure of the serum in a number of cases of nephritis, that the osmotic pressure (P) could be calculated as follows from the albumin (A) and total protein (C) concentrations in gm. per 100 ml.: $P = C\,(21{\cdot}4+5{\cdot}9A)\text{mm.H}_2\text{O}$. This formula was used for calculating the colloid osmotic pressure in our patients with Type 2 nephritis. Cholesterol was estimated by the method of Sackett (1925). Values up to 240 mg. per 100 ml. were considered normal. No figures of cholesterol are given for patients with Type 1 nephritis during the acute attack. When it was estimated it was usually normal.

Type 1 Nephritis

The acute attack. Clinical condition of the patients, and treatment. There were 40 patients in this group; they are summarized in Table I. Their ages varied from nine to 60 years, and there was no marked preponderance of any one

TABLE I

Type 1 Nephritis. Summary of Cases, with the Final Results

	Case number	Age	Sex	Day of illness on admission	Blood-pressure (mm. Hg)		Urine on discharge		Complications	Result*
					Maximum	On discharge	Blood	Albumin		
Group A	1	17	M	2	120/80	105/70	—	—	..	C
	2	22	F	3	120/60	115/70	—	trace	..	C
	3	17	M	7	170/95	125/75	—	—	Rheumatic fever	C
	4	47	M	10	180/110	140/95	—	—	..	U
	5	13	M	2	145/100	110/75	—	—	..	C
	6	44	M	7	180/90	140/80	—	—	..	U
	7	11	F	14	110/65	115/75	—	—	Pyelitis	C
	8	9	M	14	115/70	110/60	—	—	..	C
	9	31	F	21	150/85	80/60	—	—	..	C
	10	51	M	21	160/80	140/75	—	+	..	C
	11	28	F	14	125/75	110/65	—	—	..	C
Group B	12	39	M	4	165/105	120/80	—	—	..	U
	13	27	M	7	165/110	130/75	+	+	..	C
	14	22	M	7	175/95	120/75	—	trace	..	C
	15	41	M	5	170/100	120/80	—	—	..	—
	16	29	F	7	195/90	155/90	—	—	Hypochromic anaemia	U
	17	60	F	7	210/110	150/80	—	trace	..	P
	18	15	F	6	170/100	115/70	—	—	..	C
	19	35	F	6	170/110	125/80	—	—	..	—
	20	17	M	14	140/90	130/85	+	+	..	C
	21	39	M	14	180/90	135/80	—	—	..	C
	22	32	M	7	170/100	100/75	+	+	Pneumonia. Cardiac failure	C
	23	38	M	4	205/120	115/65	—	—	Pneumonia	—
	24	38	M	3	205/115	125/90	—	—	Cerebral thrombosis. Fits	U
	25	30	F	8	180/110	115/80	—	trace	Fits	C
	26	40	M	4	195/115	95/60	—	trace	Fits	—
	27	16	M	7	165/125	140/85	+	+	Fits	C
Group C	28	18	M	2	140/95	130/90	—	+	Hypochromic anaemia. Otitis media	P
	29	55	M	3	140/90	130/80	—	—	Pneumonia	P
	30	16	F	10	190/110	140/95	—	+	..	P
	31	9	F	10	180/110	110/60	—	+	Fits	P
	32	48	F	14	195/115	140/85	—	trace	Cardiac failure	C
	33	34	F	16	155/120	125/75	—	+	Pneumonia. Cardiac failure	P
	34	14	M	21	175/80	155/90	—	+	Hypochromic anaemia	P
	35	47	M	42	220/110	145/90	—	+	Hypochromic anaemia	C
	36	17	F	42	140/90	130/80	+	++	..	P
	37	58	M	90	185/120	155/85	+	++	..	P
Group D	38	15	F	5	165/120	165/120	+	+	..	D
	39	25	F	42	160/115	..	..	..	Pericarditis. Pneumonia	D
	40	38	M	120	165/100	..	..	..	Cardiac failure	D

* Result: C, cured; U, result uncertain; P, persistent symptoms; D, dead; —, no follow-up.

age-group; but only four were over 50 years old. The figures shown give no indication of the incidence in the lower age-groups, as children are not often admitted to this hospital. There were 24 males and 16 females. The onset of the illness was taken as the day when oedema or haematuria was first noticed. In all except five cases, symptoms had been present for three weeks or less when the patient was admitted to hospital. All the patients had had a respiratory infection or scarlet fever before the nephritis. The most usual infection was tonsillitis, but sometimes only a severe cold was recorded. The presenting symptom was generally oedema, which was observed at some stage in all cases except one. Haematuria and oliguria had been noticed in some patients before their admission. Dyspnoea was an important symptom in seven, all of whom were over 32 years old. Headache and vomiting had been present in some cases. One patient was admitted during an attack of convulsions. In addition to oedema of the face and limbs, some patients had fluid in the pleural cavities and abdomen, and a number had signs of pulmonary congestion. All were treated with rest in bed. The diet in severe cases for the first few days was 20 oz. of water with fruit juice, glucose, and a few biscuits. After this it was increased in such a way that the calories were raised, while the protein and sodium remained as low as possible, and the fluid intake was increased. Less severe cases received 30–40 oz. of fluid daily and a low protein, low salt diet from the start. Penicillin was given to those patients with pulmonary congestion who had a raised temperature, suggesting an active lung infection. Patients with a hypochromic anaemia received iron.

The cases of Type 1 nephritis were divided into four groups according to the severity and the course of the disease. The 11 patients in Group A either had a mild attack or had already improved considerably before admission. The 16 patients in Group B all had moderately severe nephritis, but all followed a characteristic course with a sudden diuresis, loss of oedema, fall of blood-pressure, and general improvement within two weeks of the onset. The 10 patients in Group C did not show this sudden early improvement; either diuresis and loss of oedema was gradual, or diuresis, if sudden, did not occur for several weeks. In Group D there were three patients, in all of whom the disease progressed without remission until death occurred after a few months. The patients in Group B showed the most sudden and dramatic clinical and haematological changes, and they will be discussed first and in greatest detail. The differences between these cases and those in other groups will be noted subsequently.

Course of the Acute Attack

Group B. These patients had not shown any improvement in their condition before arrival in hospital, but in several there was a rapid and sustained improvement coincident with their admission. In others, recovery was complicated by the persistence or development of cardiac, respiratory, or cerebral symptoms; thus Case 22 had pneumonia with cardiac failure, Case 23 had pneumonia, Case 24 had a cerebral thrombosis with transient hemiplegia, followed by an

attack of hypertensive encephalopathy, and Cases 25, 26, and 27 had convulsions. All, however, started to improve in two weeks or less from the onset of oedema.

The amount of fluid lost naturally varied with the amount of oedema, so that it is impossible to give absolute criteria of a good diuresis. The question was

TABLE II

Acute Type 1 Nephritis. Group B. The Extent of Diuresis as measured by the Fluid Balance and by Weight Loss

	Fluid balance (ml.)			*Body-weight*			
	Mean daily				*Weight loss*		
Case number	*1 to 3 days before diuresis*	*First 3 days of diuresis*	*Total in first week of diuresis*	*After diuresis (kg.)*	*(kg.)*	*% of final weight*	*Period (days)*
12	..	−640	−4400	62·8	10·2	16	13
13	..	−580	−3040	..	..	..	..
14	−340	−1250	−7600	51·8	6·1	12	7
15	−220	−1040	−3500	75·3	6·4	8·5	7
16	−140	−720	−2730	..	..	..	..
17	−110	−650	−5110	56·5	..	..	..
18	−340	−880	−4160	48·0	3·5	7	8
19	+560	−890	−3030	64·5	3·2	5	9
20	−490	−1260	−6160	59·5	..	..	..
21	..	−600	−1930	63·0	..	..	..
22	−190	−990	−6230	..	..	..	..
23	+10	−640	−4660	61·0	5·7	9	10
25	+170	−90	−570	74·7	1·5	3·5	7
26	−300	−710	−4860	59·2	5·0	8·5	8
27	−170	−1340	−9450	45·3	9·1	20	10
Mean	−130	−825	−4500	..	6·4	11·2	..
Number of cases	(12)	(15)	(15)	..	(9)	(9)	..

also complicated by the fact that a negative fluid balance generally appeared to be present even before loss of oedema. But when each case was considered individually, it appeared that at some point a sudden increase in the negative fluid balance occurred, which gave a clear indication of the onset of diuresis. The fluid loss in the following week, after which there was generally no oedema, could then be taken as indicating the amount of oedema fluid lost. Where the weight was recorded, a sudden fall was found when diuresis started. The mean daily fluid balance before and after the onset of diuresis, the fluid lost in the first week of diuresis, and the weight changes, are shown in Table II. Case 24 is not included, because he was incontinent for several days and too ill to be weighed. It will be seen that in all patients except one (Case 25, who had very little oedema) the mean daily fluid loss during the first few days of diuresis was over half a litre, and in several cases it was over one litre, while before the onset it had never been as much as half a litre. The loss of fluid in the first week after diuresis had started varied from 2 to 9·5 litres. Changes in weight were not often recorded for the exact week, but as there was no marked alteration in weight after diuresis was complete, this was not important. The actual losses in weight

observed varied from 1·5 to 10·2 kg., and if the final weight is taken as the normal, and the initial surplus over this value as due to oedema fluid, this fluid may be considered to have been equal to from 3·5 to 20 per cent. of the normal body weight. With the increase in urine volume, there was in most cases a reduction in the concentration of blood and albumin in the urine. In some,

TABLE III

Acute Type 1 Nephritis. Group B. Changes in the Blood with Diuresis, and the Alterations in Blood-volume calculated therefrom

	Haemoglobin (gm./100 ml.)			*Red cells (millions/c.mm.)*			*Haematocrit %*			*Mean corpuscular haemoglobin concentration %*		
Case number	*Before diuresis*	*After diuresis*	*Calculated excess blood-volume %*	*Before diuresis*	*After diuresis*	*Calculated excess blood-volume %*	*Before diuresis*	*After diuresis*	*Calculated excess blood-volume %*	*Before diuresis*	*After diuresis*	*Interval (days)*
12	12·45	12·9	7·5	4·72	..	..	34·25	38	11	36·4	34·0	7
13	10·9	13·1	20	5·02	..	..	35	41	17	31·2	32·0	9
14	14·2	15·4	8·5	5·32	5·52	4	..	..	..	..	..	10
15	14·8	17·5	18	5·21	6·11	17	41	46·25	13	36·2	38·0	4
16*	(8·9)	(12·1)	..	(3·49)	(4·52)	..	..	..	..	..	..	14
17	10·95	12·7	16	4·01	4·62	15	..	..	..	..	..	12
18	12·1	14·4	19	4·52	..	..	33·5	41	22	36·2	35·2	18
19	13·3	..	..	5·21	..	..	..	..	..	..	..	..
20	12·7	13·6	7	4·52	..	..	37	39·5	7	34·4	34·6	6
21	12·8	13·9	9	4·99	5·49	10	..	..	..	..	..	9
22	12·4	13·9	12	4·28	4·81	12	37·25	37·5	1	33·4	37·2	4
23	11·5	13·6	18	..	4·70	..	36·5	41	12	31·6	33·2	14
24	11·5	14·7	28	4·25	5·33	25	37·75	47·5	26	30·2	31·0	21
25	12·7	..	..	4·69	..	..	..	..	..	..	..	..
26	14·2	..	..	4·85	..	..	..	..	..	..	..	..
27	11·65	14·2	22	..	..	..	37·25	40	7·5	31·4	35·6	7
Mean	12·5	14·2	15	4·74	5·23	14	36·6	41·3	13	33·4	34·5	..
Number of cases	(15)	(12)	(12)	(13)	(7)	(6)	(9)	(9)	(9)	(9)	(9)	..

* Hypochromic anaemia; values not included in means.

however, there was at first an increase in the amount of blood passed. Microscopic blood and small amounts of albumin were often present for several weeks when no other signs of disordered function remained (see Table I). On discharge, blood was present in four of the sixteen cases, and albumin in eight. The blood-pressure fell as the oedema was lost. The fall was often not apparent until a day or two after the onset of diuresis. By the time of discharge all patients except two had a normal blood-pressure (see Table I).

The blood urea levels on admission and on discharge are shown in Table V. On admission, the levels varied considerably, nine patients having a normal blood urea, and the others raised values from 52 to 124 mg. per 100 ml. By the time of discharge all were normal. No correlation between the degree of nitrogen retention, as judged by blood urea, and the severity of other signs was apparent.

At the same time that diuresis occurred, marked increases in the concentration of haemoglobin and cells appeared in the blood, suggesting that as fluid was lost from the oedematous tissues it was also lost from the blood. The blood changes are shown in Table III, together with the calculated percentage changes

in blood-volume. The haemoglobin and red-cell values before diuresis were in nearly every case subnormal, which in itself suggested that the blood was diluted, since the disease had only been active for a few days; moreover, the apparent anaemia was normochromic. The increases in haemoglobin and red cell concentration, when diuresis occurred, were generally of comparable degree,

TABLE IV

Acute Type 1 Nephritis. Case 15. Changes in Weight, Blood-volume, and Blood Constituents with Diuresis which lasted from 8th to 11th day

Day of illness	*7*	*9*	*11*	*15*
1. Body-weight (kg.)	81·7	76·2	75·0	75·3
2. Blood-volume (ml.) from (3) and (6)	6,700	..	5,700	..
3. Plasma-volume (ml.)	3,950	..	3,050	..
4. Cell-volume (ml.) from (3) and (6)	2,750	..	2,650	..
5. Haemoglobin (gm./100 ml.)	14·8	14·2	17·5	16·2
6. Haematocrit (%)	41·0	..	46·25	..
7. Red cells (millions/c.mm.)	5·21	..	6·11	..
8. Mean cell-volume (μ^3)	79	..	75·5	..
Volumes expressed as %				
Blood from (2)	118	..	100	..
„ from (5)	118	123	100	108
Plasma from (3)	129	..	100	..
Cells from (4)	104	..	100	..
„ from (8)	104·5	..	100	..

but the volume of cells in the blood did not always increase proportionately. This suggested that fluid had left the cells as well as the plasma, a point which is also brought out by consideration of the rise in mean corpuscular haemoglobin concentration. The changes in blood-volume were calculated retrospectively, taking the condition after diuresis as normal or 100 per cent., and finding the increase when oedema was present. Comparison of the degree of these changes with the amount of fluid loss or percentage change in weight (Table II) shows no obvious relationship. It does not, therefore, seem that the dilution of the blood was proportional to the amount of oedema fluid in the tissues.

The extent of the calculated blood dilution was in many cases surprisingly large, being over 18 per cent. in six cases. In one patient (Case 15) this calculated change was checked by direct estimation with T 1824. The results are shown in Table IV, and it will be seen that the blood-volume, whether estimated directly or calculated from the haemoglobin concentration, was 18 per cent. above normal when oedema was present. The volume of cells calculated from the plasma-volume and haematocrit had been four per cent. above normal, and this change agrees with that found by a comparison of the mean cell-volumes. The serial haemoglobin levels, and the percentage blood-volumes calculated from them and shown in Table IV, also illustrate two points not previously mentioned. Firstly, the fall in blood-volume is not necessarily a steady one. Secondly, when diuresis is complete the haemoglobin may fall again, though not to the previous levels. These two points are best illustrated by considering two patients in whom the changes in blood-volume were calculated from the haemoglobin level at frequent intervals. The results in these two cases are shown graphically in

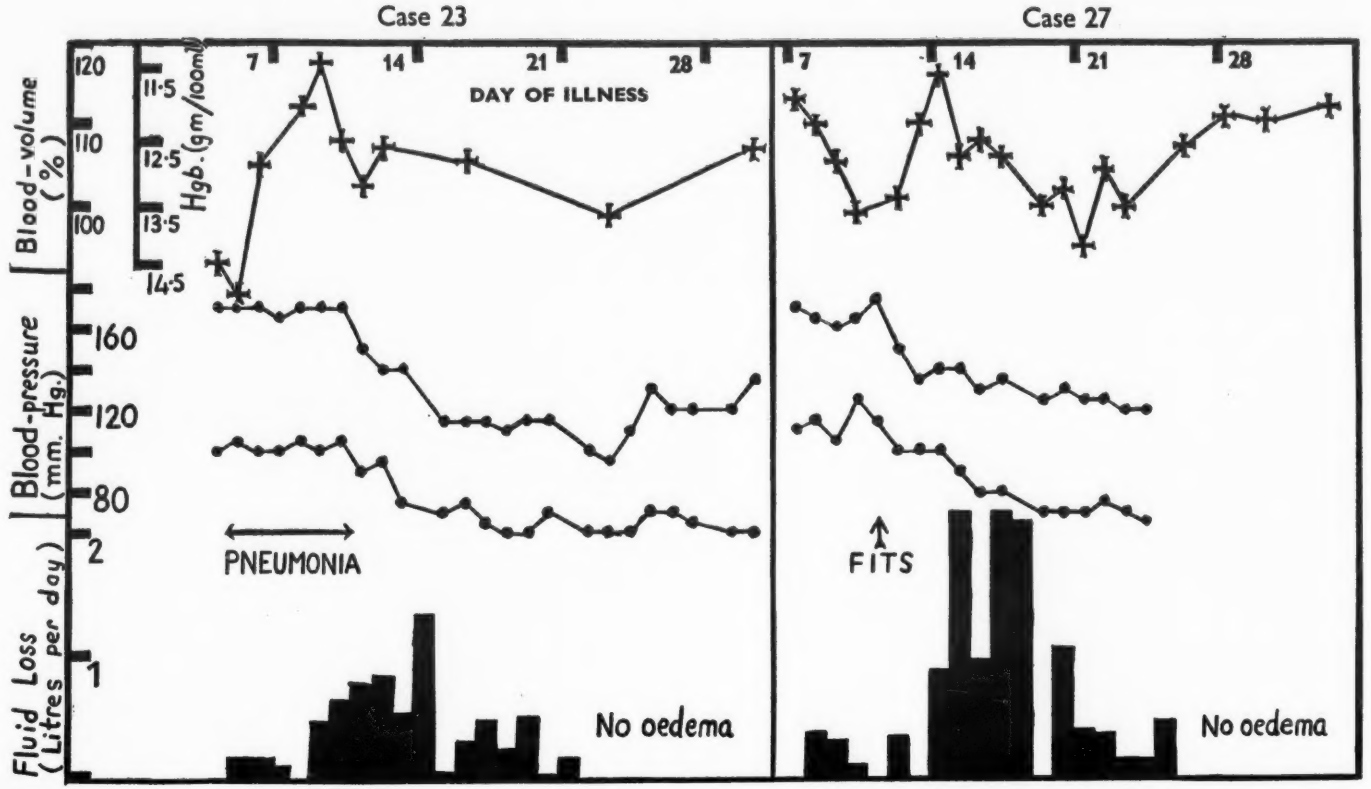

FIG. 1. Acute Type 1 nephritis. Changes in the fluid loss, blood-pressure, haemoglobin level, and blood-volume in two patients who recovered.

Fig. 1, where the percentage changes in blood-volume or haemoglobin level are compared with the blood-pressure and with the daily fluid loss, or urinary output less fluid intake.

The levels of serum-albumin and serum-globulin, before and after diuresis, are shown in Table V. Before diuresis the values for both were low in most

TABLE V

Acute Type 1 Nephritis. Group B. Changes in Serum-proteins with Diuresis and Alterations in Blood Urea

Case number	Serum-proteins (gm./100 ml.)				Interval (days)	Blood urea (mg./100 ml.)	
	Before diuresis		After diuresis				
	Albumin	Globulin	Albumin	Globulin		Initial	Final
12	2·8	2·3	2·8	2·4	10	28	..
13	3·1	2·4	3·6	2·4	9	52	40
14	3·0	2·3	..	..	..	38	26
15	3·9	2·8	4·0	2·5	5	20	..
16	..	..	..	..	..	98	32
17	3·0	2·2	3·2	3·0	12	36	..
18	3·2	2·5	..	..	..	38	30
19	..	..	..	..	..	24	..
20	3·3	2·1	3·9	2·8	20	54	26
21	4·2	2·4	..	..	..	28	..
22	3·1	2·7	3·1	2·9	20	124	34
23	3·0	2·2	2·9	2·0	19	82	40
24	2·6	2·5	3·6	2·9	36	66	34
25	..	..	..	..	..	26	..
26	2·7	2·1	3·0	2·4	25	27	..
27	2·7	2·3	4·1	2·8	30	80	34
Mean (13 cases)	3·1	2·4	..	..	..	..	..
Mean (10 cases)	3·0	2·4	3·4	2·6	..	..	..

cases. After diuresis there was generally a rise in concentration. The proportion of albumin to globulin was not, as a rule, abnormal or different at the two estimations in any one patient, and it seems probable that the change was due to alterations in the plasma-volume. The final values were, however, in many cases subnormal, suggesting that there was some degree of hypoproteinaemia.

Group A. The 11 patients in this group all made a rapid recovery. The urinary output equalled or exceeded the fluid intake from admission, and oedema, when present, was rapidly lost. No significant weight changes occurred. The urine soon ceased to contain blood, and by the time of discharge it contained albumin in only two. The blood-pressure, when raised, fell shortly after admission, and in all except one patient was normal on discharge. Other findings in this group are summarized in Table VI. The blood urea was normal in six cases, and only moderately raised in the others. The haemoglobin levels tended to be higher than in Group B, and did not alter significantly. There was some depression of serum-protein levels.

Group C. These 10 patients all improved considerably while in hospital, but the improvement was either gradual or delayed. The incidence of complications

was high. One patient had epileptiform convulsions, two had pneumonia, and one of the latter and one other had cardiac failure. Three patients had marked hypochromic anaemia. In six cases there was no sudden increase in urinary output, and the loss of oedema was gradual. In the remainder a critical diuresis did occur, but not until between the fifth and eighth weeks. All 10 patients had

TABLE VI

Acute Type 1 Nephritis. The Initial Values of Haemoglobin, Serum-proteins, and Blood Urea in the Four Groups. (*Numbers of cases in parentheses.*)

Group		*Haemoglobin* (*gm./100 ml.*)	*Serum-protein* (*gm./100 ml.*)			*Blood urea* (*mg./100 ml.*)
			Albumin	*Globulin*	*Total*	
A	Range	11·8–15·5	2·5–3·9	2·1–3·1	4·6–7·0	24–56
	Mean	13·5 (10)	3·3 (5)	2·5 (5)	5·8 (5)	41 (10)
B	Range	10·9–14·8	2·6–4·2	2·1–2·8	4·8–6·7	20–124
	Mean	12·5 (15)	3·1 (13)	2·4 (13)	5·5 (13)	51 (16)
C	Range	8·9–13·9	2·8–4·0	2·0–3·9	4·8–7·0	22–220
	Mean	11·6 (6)	3·2 (7)	2·7 (7)	5·9 (7)	83 (8)
D	Range	7·4–11·3	1·8–2·6	1·3–2·8	3·1–5·2	56–102
	Mean	9·2 (3)	2·2 (3)	2·2 (3)	4·4 (3)	74 (3)

lost their oedema on discharge. Changes in weight were not of diagnostic value in these patients, since there was wasting due to prolonged illness. In all cases the blood and albumin in the urine diminished gradually. Blood was present in only two cases on discharge, but albumin was present in all except one. The blood-pressure fell gradually, but it was still elevated in four patients at the time of discharge. The blood urea, haemoglobin, and serum-protein levels found on admission are summarized in Table VI. The blood-urea values were very variable, but tended to be higher than in Group B. All patients with abnormal values showed an improvement by the time of discharge, but five still had a blood urea above 40 mg. per 100 ml. The haemoglobin levels were subnormal on admission, and there was a more severe degree of anaemia than in Group B; in three cases the anaemia was hypochromic. When there was a critical diuresis there was a rise in the haemoglobin level due to haemoconcentration, but changes in the blood dilution were, on the whole, masked by the development of anaemia. Later, this anaemia tended to improve, but all these patients had some anaemia on discharge. The total serum-proteins tended to be slightly higher than in Group B, but this was due to globulin, the albumin levels being similar. High globulin values were found in some patients admitted early in the disease. Changes in serum-proteins during the time in hospital were not marked. In some cases there was a rise, in others a fall, but hypoproteinaemia was present in all at the time of discharge.

Group D. There were three patients in this group, all of whom died within six months of the onset of nephritis. During this time there was no improvement. The oedema remained constant or increased, and there was oliguria with albumin, blood, and casts. The blood-pressure was raised throughout, and in two cases there was a gradually increasing nitrogen retention. The haemoglobin

and serum-protein levels were low from the start. The two patients who died in hospital died of cardiac failure. Case 38 is described in the Case Reports. The findings in all three cases are summarized in Table VI.

Later Course of Type 1 Nephritis

The cases in this series have not been followed long enough to give a complete picture of the later stages of the disease when recovery does not occur. These stages, however, have been seen in others. In the majority, albuminuria persists for years, during which time the patient may be symptom-free. In this latent stage the blood picture and blood chemistry are usually normal, though renal function is gradually deteriorating. Finally renal failure develops, the blood-pressure and blood urea rise, and death occurs from uraemia or cardiac failure. The findings in this stage are similar in most particulars to those in uraemia from other causes, and will not be discussed here.

A few patients, however, have a recurrence of oedema, coupled with low plasma-proteins. Two in our present series (Cases 36 and 37) followed this course. Both had a history of sore throat followed by oedema and haematuria; they improved slowly and left hospital without oedema, but with albuminuria, hypertension, slightly raised blood urea and slightly depressed haemoglobin and serum-protein levels. Their condition then was similar to that of other cases in Group C. Eighteen and 19 months later respectively they were seen again. Case 36 now had a blood-pressure of 180/105, and there was marked oedema and albuminuria. The following values per 100 ml. were found: blood urea 44 mg., haemoglobin 10·7 gm., serum-albumin 2·7 gm., serum-globulin 2·3 gm., serum-cholesterol 370 mg. Case 37 had a blood-pressure of 200/110, with marked oedema and moderate albuminuria. The blood urea was 40 mg., haemoglobin 13·8 gm., serum-albumin 2·6 gm., serum-globulin 2·4 gm., and cholesterol 214 mg. per 100 ml. Case 36 was not seen again; Case 37 improved slowly with rest and a low sodium and high protein diet, and a year later was remaining oedema-free so long as he strictly limited his activities.

Prognosis. The results up to date are indicated in Table I. Of the 40 patients with Type 1 nephritis, three have died and four cannot be traced. Nineteen of the remaining 33, when seen three to 20 months after the onset, had no residual signs, and may be considered to have recovered. A further five patients had a raised blood-pressure but no albuminuria, so that their status is uncertain; but it is probable that the hypertension was irrelevant, as one patient was thyrotoxic and all the others were over 37 years of age. The remaining nine all had albuminuria, and therefore suffered from permanent kidney damage. Six of these had hypertension. All the mild cases in Group A recovered, with two possible exceptions. Of the 12 in Group B who were followed up, eight recovered, three are uncertain, and one has definite residual signs. Two of the 10 followed-up cases in Group C recovered, but in eight the disease persisted. All three patients in Group D died. These results suggest that the prognosis in mild cases such as those in Group A is good, that the occurrence of diuresis within a fortnight of the onset of oedema, as in Group B, is more likely to lead to complete

recovery than is a delayed or gradual diuresis (Group C), and that if oedema persists a rapid downhill course is to be expected (Group D). It is not apparent, in this small series, whether the occurrence of cardiac, cerebral, or respiratory complications had any effect on the final outcome of the disease, but it is clear that no improvement in the renal condition could be expected while an active

TABLE VII

Type 2 Nephritis. Summary of Cases

			On admission						
Case number	*Age*	*Sex*	*Week of illness*	*Blood-pressure (mm. Hg)*	*Blood urea (mg./100 ml.)*	*Urea clearance %*	*Urinary albumin (gm./litre)*	*Oedema*	*Result*
Group A									
41	34	F	9	120/65	22	66	4–20	Cleared by 16th week	Recovered
42	21	M	13	110/80	24	80	1–17	Cleared by 31st week	Recovered
43	41	M	2	125/75	30	72	2–6	Cleared by 10th week	Recovered
44	37	F	5	100/75	30	79	3–48	Cleared by 19th week	Recovered
45	19	F	3	130/65	28	86	9–12	Persistent	..
46	18	M	15	120/85	34	70	1–13	None on admission	Persistent
Group B									
47	56	M	2	155/90	26	95	½–12	Intermittent	Persistent
48	38	F	150+	135/95	30	78	½–11	Intermittent	Died after 4 years
49	42	M	4	135/95	28	70	½–10	Intermittent	Persistent
50	40	M	39	165/110	34	53	3–18	Persistent	Died after 4 years
51	25	M	13	150/85	28	43	2–22	Persistent	..
52	20	M	22	150/95	38	52	..	Persistent	..
53	19	F	35	220/145	40	30	3–12	Increasing	Died after 1½ years
54	16	F	48	150/120	22	87	12–56	Increasing	Died after 1 year
55	58	M	52	205/80	152	..	2–22	Increasing	Died after 1½ years
56	22	M	4	155/100	44	56	..	Persistent	Died after 1 year
57	37	F	40	200/120	58	32	½–24	Persistent	Died after 1 year
58	42	F	113	185/110	70	26	6–15	Persistent	Died after 2½ years
Group C									
59	47	M	3	180/100	78	27	3–16	Persistent	..
60	58	M	3	140/95	88	27	1–36	Persistent	Died after 22 weeks
61	25	M	1	125/80	98	30	65	Persistent	Died after 6 weeks

lung infection was present. When this was effectively treated with penicillin, no serious delay in general improvement was noticed.

Although at first it was not possible to distinguish either clinically or biochemically the cases which later did well from those which did not, when the cases were divided into groups according to their progress it was found that in the group with delayed improvement, and in that in which no improvement

occurred, there were patients with very low initial haemoglobin or serum-protein levels. These were not necessarily patients admitted late in the attack, and the explanation is not apparent. It should be noted that Van Slyke (1930) also found that low plasma-proteins indicated a poor prognosis.

Type 2 Nephritis

Clinical condition of the patients on admission, and treatment. Twenty-one cases of Type 2 nephritis have been studied, and are summarized in Table VII. The patients' ages varied from 16 to 58 years, and were evenly distributed between the five decades. There were thirteen males and eight females. The disease was characterized by the insidious onset of oedema without other symptoms. The duration, calculated from the date when the oedema was first noted, varied when the patients were first seen from a week to over three years. The severity of the disease bore little relation to the length of illness; in some it ran a rapid course, and in others it remained stationary for months. In only two cases was there a history of an infection shortly before the onset of oedema, one patient having had a cold, and one pneumonia. In addition to the oedema, which was present on admission in all cases except one, there was in every case gross albuminuria. Blood was not present to naked-eye examination, but it was seen microscopically in the urine of all but four of the 21 cases. Pus cells were always present, and usually hyaline and granular casts. Several patients had ascites and pleural effusion as well as oedema.

All patients with severe oedema were kept in bed. They were given a high protein, low salt diet containing approximately 125 gm. of protein and 1·2 gm. of sodium a day. Those who were very ill, and were unable to take the full diet, received less than the above quantities. The fluid intake was usually limited to 40 oz. daily. Other forms of treatment, temporarily employed in some cases, were a high fluid intake (140 oz. daily), and intramuscular neptal. No treatment produced consistent results, and when recovery occurred it usually appeared to be unrelated to the treatment.

Course of the Disease

In Table VII the cases are divided into three groups according to their condition when first seen. In Group A there were six patients in whom the blood-pressure, blood urea, and urea clearance were within normal limits. The patients who recovered were all in this group. In Group B there were 12, all of whom had hypertension when first seen, and some of whom had nitrogen retention. In all of these the disease was progressive. In Group C there were three patients; these were all seen shortly after the onset of oedema, but even then they had severe renal failure, and they deteriorated very rapidly.

Patients who recovered. Cases 41, 42, 43, and 44 all eventually lost their oedema and albuminuria. Recovery was slow, and not complete when they left hospital, so that prognosis was not certain. The findings in these four cases are summarized in Table VIII, and those in Case 44 are shown graphically in Fig. 2.

All these patients had a good diuresis while in hospital, losing from 9 to 15 kg. in weight. With the diuresis there was usually a lowering of the concentration of albumin in the urine, but the total amount excreted did not lessen appreciably for some weeks. The duration of albuminuria cannot be given exactly, as the patients were only seen infrequently after their discharge, and the times given

TABLE VIII

Type 2 Nephritis. Findings in the Patients who Recovered

	Week of illness	Weight (kg.)	Haemoglobin (gm./100 ml.)	Red cells (millions/c.mm.)	Serum-proteins (gm./100 ml.) Albumin	Serum-proteins (gm./100 ml.) Globulin	Colloid osmotic pressure (mm. H_2O)	Blood-cholesterol (mg./100 ml.)
Case 41								
On admission	9	82·8	16·0	6·03	3·0	2·3	205	344
After diuresis	13	68·0	14·8	5·42	3·1	2·1	205	486
On discharge	16	68·2	..	..	2·75	2·65	203	535
Albumin-free	31	..	..	..	..	..	..	..
Case 42								
On admission	13	81·0	14·8	5·15	2·6	2·7	194	484
After diuresis	21	72·0	..	..	2·3	3·3	195	498
On discharge	31	79·0	..	..	3·2	2·6	234	362
Albumin-free	42	..	..	..	..	..	..	..
Case 43								
On admission	2	..	16·3	5·72	2·5	2·5	181	430
On discharge	10	..	..	..	2·7	2·4	190	..
Albumin-free	125	..	..	..	..	..	..	..
Case 44								
On admission	5	67·7	16·9	5·69	2·0	2·4	146	1,540
After diuresis	11	57·8	15·4	5·42	2·2	2·5	171	830
On discharge	19	57·3	13·3	4·69	2·8	2·6	205	800
Albumin-free	36	..	12·6	..	4·0	3·0	315	385

in Table VIII are the first occasion on which no albumin was found. The blood-pressure, blood urea, and urea clearance were normal throughout in all these patients. The haemoglobin and red cell concentrations were high when they were first seen, the haemoglobin being 16·0 gm. or more per 100 ml. in three cases. Shortly after diuresis there was, in two cases, a fall in concentration. No direct estimations of blood-volume were made, so that it is not possible to say with certainty whether these changes were due to alterations in concentration of the blood, but the high initial values indicate that in this type of nephritis the oedematous stage is not accompanied by hydraemia.

The serum-proteins, especially albumin, were reduced in amount. The colloid osmotic pressure calculated from the serum-proteins was from 146 to 205 mm. H_2O while oedema was present. When the oedema was lost, in three of the four cases there was no significant change in the colloid osmotic pressure, and in the fourth it was still only 171 mm. H_2O. All these levels were still abnormal when the patients left hospital. The blood-cholesterol was raised in every case,

Case 44 having as much as 1·5 gm. per 100 ml. In this instance there was a fall with diuresis, but Case 41 showed a rise, and Case 42 no change. High levels were still present on discharge, and Case 44, 36 weeks from the onset, when free

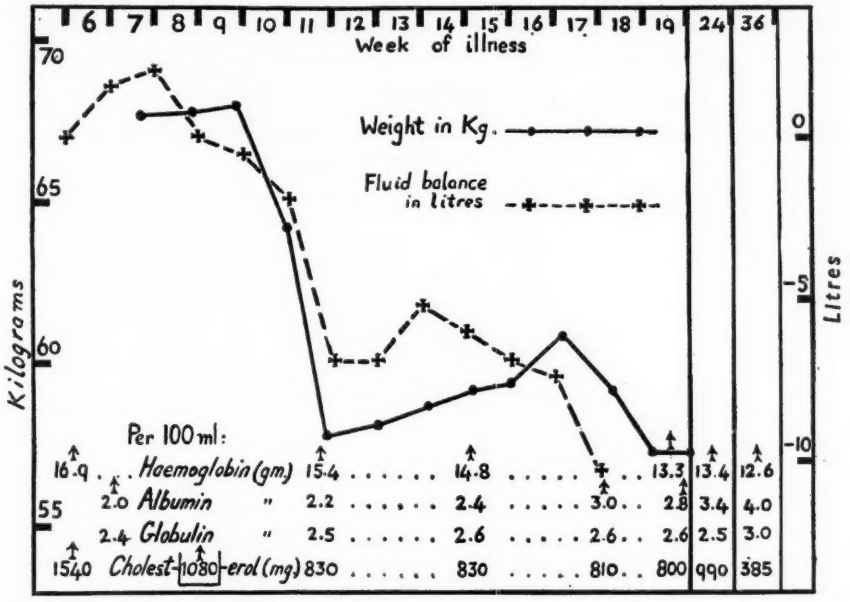

FIG 2. Type 2 nephritis. The fluid balance and body weight of Case 44, who recovered, together with the haemoglobin, cholesterol, and serum-protein levels.

of albuminuria and normal in all other respects, still had a blood-cholesterol of 385 mg. per 100 ml.

Patients with persistent disease (*Cases 46 to 58*). These 13 patients were never free of pathological signs, and all those who have been followed died from one to four years after the first appearance of oedema. Oedema occurred in all, but it was sometimes intermittent; Case 46 had none on his admission to hospital, and Cases 47 and 48 had only slight oedema of the ankles on discharge. In all these patients oedema reappeared later. In others it increased steadily until death. The urine always contained albumin. The amount varied considerably from day to day, without any apparent relation to the state of oedema or to the urine volume. The blood-pressure was normal in Case 46 when he was first seen. Later it rose. All the other patients were hypertensive. It is possible that if they had been seen earlier a normal blood-pressure might have been found, but since some were seen within a few weeks of the onset of oedema, it is doubtful whether the oedema preceded the hypertension. Once hypertension had developed, normal blood-pressures were not regained.

The blood-pressure, blood urea, and urea clearance were the most valuable signs for following the progress of these cases, and the varying condition of the patients on admission can be seen by comparing these data in Table VII. In

spite of a raised blood-pressure, so long as kidney function remained good there was no immediate danger to life, but in the cases which were followed up uraemia eventually developed. In Table IX later blood-urea values are given, showing in some cases the terminal rise. This rise was not always steady, but once raised, the blood urea was never again normal. The haemoglobin and

TABLE IX

Type 2 Nephritis. Group B. The Relation of Haemoglobin and Red Blood-cell Levels to the Level of the Blood Urea

Case number	*Duration of illness (weeks)*	*Haemoglobin (gm./100 ml.)*	*Red blood-cells (millions/c.mm.)*	*Blood urea (mg./100 ml.)*	*Log. of blood urea*
47	2	14·5	5·02	26	1·41
48	150+	12·7	4·82	24	1·38
49	4	16·6	5·75	28	1·45
50	39	14·5	5·21	34	1·53
	56	11·2	4·20	48	1·68
	58	10·9	4·01	56	1·75
	99	14·9	..	46	1·66
	107	13·2	..	64	1·81
	116	9·6	..	62	1·79
	156	8·9	..	82	1·92
	164	6·2	..	174	2·24
51	13	13·6	4·31	28	1·45
	19	10·7	4·00	34	1·53
	25	9·5	3·52	46	1·66
52	22	13·3	4·91	38	1·58
53	35	9·2	3·25	40	1·60
	79	7·4	2·72	164	2·21
54	48	14·5	5·02	22	1·34
	55	10·4	3·72	108	2·03
55	52	8·3	2·81	164	2·21
56	4	13·6	4·72	44	1·64
	34	11·2	4·01	54	1·73
	36	7·4	2·62	106	2·02
	40	4·4	1·50	200	2·30
57	40	9·8	3·80	58	1·76
	47	8·0	3·10	88	1·94
58	113	11·8	4·45	70	1·84
	118	9·2	3·29	226	2·35

erythrocyte levels of these patients are also shown in Table IX. So long as the blood urea was normal, these remained within normal limits, and did not show any consistent change when oedema was lost. But there were considerable short-term changes in haemoglobin concentration, not related to fluid output. Thus Case 48 showed the following values in gm. per 100 ml.: on admission, 14·5; after 2 weeks, 12·1; 4 weeks, 13·9; 5 weeks, 12·0; 6 weeks, 13·1. During this time she was in positive fluid balance, and gained 10 kg. in weight. It is difficult to explain these changes except by assuming changes in blood concentration. When the blood urea rose, the haemoglobin and red-cell count fell, and a normochromic anaemia developed. The haemoglobin level was not inversely proportional to the blood urea: the latter rose more rapidly than the former fell. But when the haemoglobin level was compared with the logarithm of the blood urea, a close linear relationship was found. The values are plotted in Fig. 3. The

correlation coefficient of the haemoglobin with the logarithm of the blood urea was 0·78 (standard error 0·074). The regression coefficient calculated from these figures was 7·5. This meant that a mean fall of 0·75 gm. per 100 ml. of haemoglobin took place with every rise of 0·10 in the logarithm of the blood urea.

The serum-proteins are shown in Table X. On admission, the albumin was low in nearly every patient, being less than 3·0 gm. per 100 ml. in all except two.

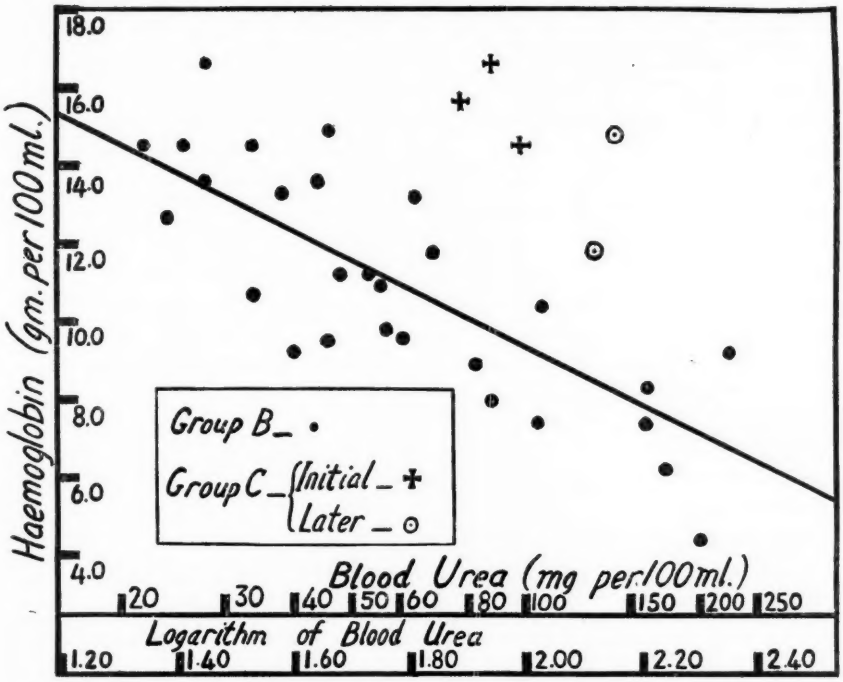

Fig. 3. The relation of the haemoglobin level to the blood urea level in cases of Type 2 nephritis. The straight line is the regression line found by the method of least squares from the values in Group B. The regression equation is $y = 24{\cdot}2 - 7{\cdot}5\,x$ where y = haemoglobin and x = log. blood urea.

The globulin level was low to normal, except in one case where it was 3·7 gm. per 100 ml. After varying periods in hospital on a high protein diet the changes were not great, but there was a tendency for the higher albumin levels to be lower, and for the lower globulin values to be higher. When the colloid osmotic pressures were calculated from the protein values, it was seen that a fall had occurred in the cases where these pressures were initially above 170 mm. H_2O, while pressure which had been below 170 mm. H_2O showed a rise. It seemed that on this diet it was possible to maintain the proteins at a level giving an osmotic pressure of 170 mm. H_2O, but not higher. Just as in the cases who recovered, there was no apparent relation between the presence of oedema and the colloid osmotic pressure. Case 47 lost 7·2 kg. of weight in four weeks, and then had little oedema, yet the osmotic pressure had fallen from 244 to 183 mm.

H_2O. The blood-cholesterol levels were, with one exception, raised. They varied considerably, and did not stay constant in any one patient. Their changes could not be correlated with alterations of oedema or of serum-proteins.

Patients with rapidly progressive signs. Group C. These three patients were all admitted within three weeks of the onset of oedema, but their condition was

TABLE X

Type 2 Nephritis. Group B. Serum-protein and Blood-cholesterol Levels

Case number	Serum-protein (gm./100 ml.) Initial Albumin	Initial Globulin	Final Albumin	Final Globulin	Colloid osmotic pressure (mm. H_2O) Initial	Final	Time (weeks)	Blood-cholesterol (mg./100 ml.) Initial	Final	Time (weeks)
47	3·5	2·3	2·6	2·4	244	183	4	570	435	10
48	2·7	2·9	2·3	2·5	208	167	13	326	405	12
49	3·3	2·8	3·0	2·3	250	207	8	255	240	5
50	2·3	1·9	2·5	2·8	146	191	23	452	530	13
51	2·0	1·9	1·9	2·6	129	145	8	290	450	8
52	2·8	2·2	2·7	2·5	170	194	2	378	305	2
53	2·5	2·8	..	..	191	..	..	..	..	..
54	2·6	2·4	1·7	2·0	183	116	7	280	..	..
55	2·7	3·7	..	..	238	..	..	190	..	..
56	2·6	2·1	2·7	2·1	173	179	2	402	..	..
57	2·2	2·5	2·4	2·6	162	178	7	495	495	7
58	1·2	1·8	1·9	2·6	85	147	5	280	278	2
Mean	2·5	2·4	2·4	2·4	182	171	..	356	392	..
Number of cases	(12)	..	(10)	..	(12)	(10)	..	(11)	(8)	..

TABLE XI

Type 2 Nephritis. The Findings in Group C

Case number	Week of illness	Serum-protein (gm./100 ml.) Albumin	Globulin	Colloid osmotic pressure (mm. H_2O)	Blood-cholesterol (mg./100 ml.)	Haemoglobin (gm./100 ml.)	Red blood-cells (millions/c.mm.)	Blood urea mg./100 ml.	Log.
59	3	2·5	2·3	173	515	15·7	5·51	78	1·89
	4	..	..	..	..	..	..	64	..
60	3	2·6	2·3	180	418	16·6	5·72	88	1·94
	8	2·6	2·0	169	412	14·8	5·07	142	2·15
	12	2·2	1·8	137	390	11·8	4·13	130	2·12
61	1	2·7	2·1	179	455	14·5	5·21	98	1·99
	5	..	..	..	..	..	..	88	..

in many ways similar to that of the patients in Group B when after months of illness they had developed terminal uraemia. There were, however, differences which suggested that the illness was a recent one, and not the final stage of a long-standing unrecognized condition. One patient died after six weeks, another after 22 weeks, and one was still alive after eight months. Oedema was marked and persistent in all cases. The albuminuria was heavy, being as much as 6·5 gm. per 100 ml. in Case 61. The blood-pressure was raised in two cases, but normal in Case 61. Changes in the blood are shown in Table XI, and were as

follows: The blood urea was raised in each case, and the urea clearance was 27 to 30 per cent. In spite of this, the haemoglobin and red blood-cell levels were initially normal. The haemoglobin levels have been plotted against the logarithm of the blood urea in Fig. 3, and it is seen that the relationship between haemoglobin and blood urea, which is so clear in Group B, was not apparent in Group C. This suggests that the uraemia had developed rapidly, so that there had been no time for anaemia to occur. In Case 60, a patient who was observed for several weeks, anaemia did develop, and by the 12th week the relation between haemoglobin and blood urea was similar to that in Group B. Both serum-albumin and serum-globulin were low in all patients on their admission, and in Case 60 they fell steadily during the nine weeks of observation. The blood-cholesterol was high in all.

Prognosis. Four of the six patients who had a normal blood-pressure when first seen later became free of oedema and albuminuria; one has not yet been adequately followed, and in one the disease progressed. All the patients who had hypertension died in four years or less from the onset. Those who were seen with uraemia early in the disease had a short expectation of life, two of them dying within six months.

Discussion

The following pictures may now be drawn of the changes which occur in Type 1 and Type 2 nephritis. The patient with Type 1 nephritis, one to two weeks after an acute respiratory infection, develops oliguria, albuminuria, and haematuria. The failure to excrete water results in a generalized hydration, which is shown by oedema of the tissues and hydraemia, manifest as a fall in haemoglobin, red cell, and serum-protein concentration. At the same time there is a failure of adequate nitrogen excretion, shown by the raised blood urea level. The blood-pressure is raised at this stage. In most cases, within a fortnight of the onset of oedema there is a sudden recovery of the power to excrete water, and fluid is lost from the body, with loss of oedema and restoration of a normal blood-volume. The blood-pressure becomes normal at the same time, or a few days later, and so does the blood urea. Some residual kidney damage is shown by the presence of albumin and blood in the urine, but in most cases these disappear after some weeks, and from that time recovery may be said to be complete. In other cases diuresis takes place after several weeks, and may be gradual, not sudden. Some of these patients never lose their albuminuria. A third small group never show any improvement in water excretion. The oedema remains stationary, though after a time the hydraemia is lost. The blood-pressure remains high, and nitrogen retention may increase. Death in these cases occurs within a few months.

The anaemia which is often present early in the acute attack is due to blood dilution, but if the attack is prolonged a true normochromic anaemia develops. The patients who improve, but still have albuminuria, generally pass into a symptomless latent stage that may last for years before renal failure develops. A few, however, become oedematous again. At this stage there is no hydraemia,

the serum-proteins are low and the cholesterol high, so that the condition is similar to that found in Type 2 nephritis.

The patient with Type 2 nephritis develops oedema without any contributory illness. At the same time albuminuria is found, with hypoproteinaemia and cholesterolaemia, all of which may have been present before the oedema. There is no anaemia, and the high haemoglobin and red cell levels suggest that the plasma-volume is normal or subnormal. Some patients have at first a normal blood-pressure and no signs of nitrogen retention, but others have hypertension, or hypertension and urea retention, so early that they may have occurred at the same time as the oedema or before it. The oedema may persist for months, with fluctuations which are not related to alterations in any of the estimated blood constituents. Some of the patients with a normal blood-pressure, after varying times, lose their oedema, the diuresis lasting for several weeks and occurring without any consistent change in the albuminuria, serum-proteins, or blood-cholesterol. The blood chemistry returns gradually to normal, and the albuminuria slowly diminishes and is finally lost. The last abnormal sign is perhaps cholesterolaemia. The haemoglobin level remains within normal limits, but may be lower after diuresis than at the start. All the other patients, after a varying time, develop hypertension, and finally uraemia. Those in whom both these signs are present from the start deteriorate very rapidly. When the patient becomes uraemic there is a fall in the haemoglobin and red cell content of the blood, the level being inversely related to the degree of urea retention.

Ellis's (1942) differentiation of nephritis into two unrelated types is thus clearly supported by these two very different pictures of disordered physiology. The acute attack of Type 1 nephritis and the early case of Type 2 nephritis can be differentiated as clearly by a chemical and physical study of the blood as they can by the clinical history and findings. The position is not quite so clear when the later course of Type 1 nephritis is considered. Ellis describes four possible courses: recovery, death in the acute attack, rapid deterioration with death in a few months, and persistent albuminuria with death after a latent period, often of years, from hypertension and renal failure. In the present series there were no deaths during the acute attack, but the other three courses were all observed. But in addition there were a few patients who, during the latent stage, again developed oedema, this time similar in nature to the oedema of Type 2 nephritis. While such a course is not recognized by Ellis, it is that described by earlier workers. Volhard and Fahr (1914), Volhard (1918), and Addis (1925 and 1928) classified nephritis into three types—haemorrhagic or glomerular, arteriosclerotic or nephrosclerotic, and degenerative nephritis or nephrosis, and considered that patients with haemorrhagic nephritis—that is, with acute Type 1 nephritis—sometimes pass into a stage of 'active chronic nephritis' with oedema and marked albuminuria, and that at this stage the condition is indistinguishable from nephrosis. It is this condition which obscures the differentiation of the two types, and which has led to the view that all cases of Type 2 nephritis are only a stage in the development of acute glomerular nephritis—the stage of subacute nephritis. The condition of the patients during this stage does not in any way

differ from that found in Type 2 nephritis, but the history is usually distinctive. There are patients, however (Case 56 is an example) in whom, although there is a definite history of acute nephritis, when death occurs during a hypoproteinaemic oedematous phase the kidney changes are found to be typical of Type 2 nephritis. The example here given is described by Davson and Platt (1949), who record two others of the same kind. The relation of this condition to Type 2 nephritis is thus by no means clear, but it is certain that it occurs, and that it follows acute Type 1 nephritis.

Two types of oedema occur in nephritis, the one in the early stages of acute Type 1 nephritis, and the other in Type 2 and in the later stages of Type 1 nephritis. The first is characterized by hydraemia, with dilution of the haemoglobin and serum-proteins. The second is characterized by low serum-proteins and high blood-cholesterol. The relation of blood-volume changes to oedema formation has been investigated by a number of workers, but the earlier work is difficult to interpret, as it is not usually clear to what type of nephritis, or to what stage of the disease, the investigations refer. They have been summarized by McClure, de Takáts, and Hinman (1933). MacArthur (1942) followed 21 cases of acute haemorrhagic nephritis in children, with serial haemoglobin estimations and red cell counts. The initial values were low. Immediately after diuresis there was a sharp rise in both levels, and then a slow fall. These results agree with those of the present investigation, but the interpretations differ. Although MacArthur stated that there was no reason to suppose an absolute deficiency of haemoglobin or of red cells in this type of anaemia, he considered that initially the blood-volume was normal, and that as a result of diuresis there was a concentration, followed by a restoration of normal volume. This view found support in a later paper (MacArthur, 1946) where the plasma-volumes, estimated with Congo red, were considered to be normal before diuresis, to fall to subnormal values during diuresis, and to return to normal afterwards. No data were given as to the cell-volumes, so that it is possible that the final rise in plasma-volume may have been compensatory to a fall in cell-volume as true anaemia developed. Cardozo (1946) followed 18 cases of acute haemorrhagic nephritis; in five the plasma-volume was estimated with T 1824 before and after diuresis, and in four there was a fall in volume with loss of oedema. In the majority of cases a marked increase in the haematocrit readings also indicated haemoconcentration. There is thus considerable support for the view that the plasma-volume is increased during the oedematous stage of acute Type 1 nephritis, and that it returns to normal with diuresis. The failure appears to be one of water excretion. The water is presented to the kidney but is not eliminated. This view is contrary to the theory, frequently advanced, that the oedema of acute nephritis is due to fluid leaving the blood owing to increased capillary permeability, and so not being available for excretion.

Changes in the blood-volume in Type 2 nephritis, or in conditions which we may assume to have been the same disease, were studied by McClure, de Takáts, and Hinman (1933) and by MacArthur (1946). The former workers did not estimate blood-volume directly, but made detailed studies over long periods

of the changes in the red cells, haemoglobin, cell volume, and total blood solids. They found that the plasma-volume was apparently below normal as oedema advanced. When oedema was stationary it rose to normal levels, and maintained these levels during and after diuresis. In any one case, the plasma-volume was always higher when oedema was stationary than when it was increasing, but the volumes during and after diuresis were variable. MacArthur (1946) estimated plasma-volumes with Congo red in five cases of the nephrotic syndrome in children, and found that while oedema increased and after it was lost the volumes were similar, but that during diuresis they were raised. Both accounts therefore agree that the oedema of Type 2 nephritis is not accompanied by hydraemia, as is the case in acute Type 1 nephritis. This finding might be considered to give support to the theory which attributes oedema formation in Type 2 nephritis directly to low serum-protein concentration and to the resulting low colloid osmotic pressure of the blood. The colloid osmotic pressure draws water from the tissues against the capillary pressure, and when it is reduced the water accumulates in the tissues until stopped by tissue tension, and is not available for excretion. This theory, originally put forward by Epstein (1917), is still the standard explanation of the occurrence of oedema in this variety of nephritis, and appears in recent standard text-books of applied physiology, in spite of the considerable weight of evidence against it. If the oedema is primarily controlled by the osmotic pressure of the serum-proteins, it is clear that it should vary with protein level, but there is little evidence of any quantitative relationship between the serum-protein level and the occurrence or extent of oedema. Moore and Van Slyke (1930) considered the relationship of the absence or presence of oedema, in 75 cases of nephritis, to differences in serum-protein levels. They found that the critical levels below which oedema was likely to occur were 2·5 gm. per 100 ml. of albumin or 5·5 gm. per 100 ml. of total protein, but it was not always present below these levels or absent above, and they recognized that some other factor must be operative. McClure, de Takáts, and Hinman (1933) reviewed the subject thoroughly, and also followed the changes in nine children with the nephrotic syndrome. They found there was at the most only a slight increase in serum-proteins when oedema was lost, and that for some time after its loss the level was below that at which oedema was expected to occur. They concluded that while a low concentration of the plasma-proteins might be a factor favouring the formation of oedema, some other factor was necessary to bring it about. The present results confirm that conclusion. The three patients who completely lost their oedema did so without a significant rise in colloid osmotic pressure, and in other cases there was no correlation between changes in osmotic pressure and changes in oedema. It is clear, therefore, that some other explanation of oedema formation in Type 2 nephritis must be found.

The occurrence of mild anaemia in acute Type 1 nephritis is well established. Thus Ellis (1942) found a haemoglobin level of less that 70 per cent. and a red cell count of less than 4·5 million per c.mm. in a third of his 225 cases. The part played by haemodilution in the production of this anaemia has already been

discussed, but it is still necessary to account for the true anaemia which develops, particularly in prolonged cases. It has been suggested that it is caused by the loss of blood in the urine. Two things are against this. Firstly, it was found that a very blood-stained urine, resembling that seen in a severe attack, could be produced by adding less than 1 ml. of blood to a 24-hour specimen of urine. The loss of blood can therefore only be slight. Secondly, the anaemia is normochromic, while that which follows prolonged blood loss is hypochromic. Emerson (1948) recorded a case of acute Type 1 nephritis in which a rapidly progressive anaemia was shown by the Ashby transfusion technique (Ashby, 1919) to be haemolytic in origin. The degree of anaemia in this case was, however, greater than usual, and there is little evidence to suggest that haemolysis commonly occurs. The remaining possible explanation of the anaemia is that it is due to depressed marrow function. Leitner (1949) examined the sternal marrow in four cases of acute nephritis, and found that after a few weeks of illness there was a hypoplastic picture.

The contrasting normal blood picture in early Type 2 nephritis is often one of the factors in establishing its diagnosis from Type 1 nephritis, but this difference is lost when uraemia develops. Anaemia as a complication of uraemia is well recognized, and has been studied extensively (Brown and Roth, 1922; Townsend, Massie, and Lyons, 1937). Here again blood loss has been suggested as a cause, but as Brown and Roth showed (1922), the loss is in many cases quite inadequate as an explanation. Haemolysis has been suggested, but the evidence, summarized by Leitner (1949), is largely against this. Again the most probable explanation is deficient blood formation. Leitner (1949) reviewed the work which had been done on this point; in most cases erythropoietic hypoplasia, or delayed maturation of the red cell series, was demonstrated. He also recorded his own observations of six patients with chronic uraemia, in whom he found hypoplasia, but rarely aplasia, of bone-marrow erythropoiesis; leucopoiesis and megakaryocyte production were unaffected.

Case Reports of Type 1 Nephritis

Case 23 (Group B, Fig. 1). This patient, a man of 38 years, was admitted on the fourth day after the onset of oedema, and was very ill, with considerable oedema and respiratory distress. The next day he was pyrexial, with signs of an acute respiratory infection. This was treated with penicillin, and by the 10th day the temperature was normal and the chest clearing. There was no improvement in the renal condition until the ninth day, when the urinary output was for the first time significantly greater than the fluid intake. Thereafter the output rose steadily, the fluid loss being 1,300 ml. on the 14th day. The blood-pressure remained about 170/100 until the 11th day and then fell, reaching 115/70 on the 15th. The haemoglobin was 14·5 gm. per 100 ml. on admission, 15·2 gm. per 100 ml. the next day, and fell to 11·5 gm. per 100 ml. on the ninth, but rose with diuresis to 13·6 gm. per 100 ml. on the 23rd day. By the 30th day it had fallen again to 12·7 gm. per 100 ml. Thus there appeared to be a steady rise in the blood-volume until the ninth day, and then a fall until diuresis was complete. The final fall in haemoglobin concentration should probably not be interpreted as being due to an alteration of blood-volume, but to the emergence

of a true anaemia which had previously been masked by the blood-volume changes. This is the more likely since the post-diuresis value of 13·6 gm. per 100 ml. was considerably less than that of 15·2 gm. on the fifth day of the illness, when there was probably already some blood dilution. It should be noted that if anaemia had been developing throughout, it would have had the effect of making increases in blood-volume appear less.

Case 27 (Group B, Fig. 1). This boy of 16 years was admitted seven days after the onset of oedema. Oedema was marked, and the urinary output low, with much blood and albumin. His condition remained unchanged until the 10th day, when he had an attack of hypertensive encephalopathy. On the 14th day diuresis started, and on the 15th, 17th, and 18th days he passed over two litres more urine daily than he drank fluid. By the 21st day there was no oedema, and it did not recur. The blood-pressure, which was 170/110 on admission and 175/115 on the day of the fits, fell thereafter reaching 125/70 on the 19th day. The haemoglobin, which was 11·9 gm. per 100 ml. on admission, rose to 13·65 gm. per 100 ml. on the 10th day, although there had been no diuresis. It fell again to 11·65 gm. per 100 ml. on the 14th day. When diuresis started it rose again, reaching 14·2 gm. per 100 ml. on the 21st day. After this, as in Case 23, it fell, and remained about 12·0 gm. per 100 ml. till his discharge from hospital. Two months later it was 13·8 gm. per 100 ml. It appears from this that on his admission the blood-volume was raised, and that it fell at first in spite of the lack of diuresis, this phase culminating in a hypertensive attack. Then it rose again until the onset of diuresis, when a steady fall set in. The final fall in haemoglobin levels should probably be interpreted again as being due to anaemia, not to blood dilution.

Case 38 (Group D). This girl of 15 years was admitted five days after the onset of oedema, and two weeks after a cold and sore throat. She had oedema of the face, ankles, and sacrum. She had oliguria, and the urine contained many red blood-cells, casts, and pus cells, and up to 2 gm. of albumin per 100 ml. This urinary condition persisted throughout. The blood-pressure remained at 150 to 165 systolic, and 90 to 95 diastolic. The blood urea was 56 mg. per 100 ml. on her admission, but later fell to 34 mg. per 100 ml. The haemoglobin was very low (11·3 gm. per 100 ml.) on admission. It varied considerably in the first fortnight, rising to a maximum of 12·2 to 12·6 gm. per 100 ml. on three occasions, but falling after each rise to 10 to 11 gm. per 100 ml. These variations were probably due to changes in blood-volume. After this there was a steady fall of the haemoglobin level, which was 7·3 gm. per 100 ml. after five weeks, suggesting the development of a true anaemia. From five to nineteen weeks it rose slowly to 10·5 gm. per 100 ml. Since there was no general improvement, it is possible that this change was due to loss of fluid from the blood. The colour index was normal throughout. The serum-proteins were extraordinarily low on admission: albumin 1·8 gm. and globulin 1·3 gm. per 100 ml. They improved slightly at first, being 2·9 gm. and 2·0 gm. respectively per 100 ml. after 10 days, but later there was a fall in albumin and a rise in globulin. The patient died at home, 25 weeks from the onset.

My thanks are due to Professor R. Platt for his advice and criticism during this work, and to the Clinical Laboratory of the Manchester Royal Infirmary for carrying out the biochemical estimations.

Summary

1. A study has been made of 40 cases of Type 1 nephritis and 21 cases of Type 2 nephritis. Throughout the course of the diseases estimations have been made of the haemoglobin and red cell levels, the serum-proteins, blood-cholesterol, and blood urea.

2. When the observed changes in these constituents are related to the clinical condition of the patients, in particular to water retention or loss, it is seen that the pictures of disordered physiology found in acute Type 1 nephritis and in Type 2 nephritis are completely different, although both result in oedema.

3. In the oedema of acute Type 1 nephritis water is present in excess both in the tissues and in the blood, the latter being increased in volume in some cases by 18 per cent. or more. This results in a dilution of the blood constituents, but in the early stages of the disease there is seldom a fall in the absolute amount of haemoglobin or of serum-protein.

4. In Type 2 nephritis there is no excess of water in the blood when oedema is present, and the haemoglobin level is at first high. The serum-protein levels are low, but the absence of any consistent relationship between changes in these levels and alterations in water balance makes it clear that the oedema cannot be due to lowered colloid osmotic pressure alone.

5. In Type 1 nephritis in the acute stage, the apparent anaemia is due to blood dilution, but when recovery is delayed a true anaemia develops. In Type 2 nephritis anaemia is unusual until the final stage of nitrogen retention is reached, when as the blood urea rises a normochromic anaemia develops.

6. A considerable proportion of the patients with Type 1 nephritis in this series recovered. The majority of these had a marked and sudden diuresis within two weeks of the onset of oedema. Very few patients with Type 2 nephritis recovered. Recovery was not observed once hypertension or nitrogen retention had developed.

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616–005.98 : 616.12–008.46

THE ORIGIN OF OEDEMA IN HEART FAILURE[1]

By JAN BROD and ZDENĚK FEJFAR

With the technical assistance of Evženie Kotanová

(From the First Medical Clinic, Charles University, Praha, and the Department of Medicine, State Hospital, Motol-Praha, Czechoslovakia)

Introduction

The genesis of cardiac oedema is a long-disputed problem. Ten years ago it seemed that the question had been solved in favour of Starling's (1912) back-pressure theory, which attributed the formation of oedema to an increase in venous pressure due to diminished cardiac competence. Recent years have produced new experimental facts which do not fit into Starling's scheme and which seem to revive, though in a modified form, the 'forward failure' theory. Thus Starr, Jeffers, and Meade (1943) found no conspicuous rise in venous pressure after searing the right ventricle of a dog with a red-hot iron. Similarly, Warren and Stead (1944) observed that in some cardiac patients the body-weight increased after the administration of salt before any significant rise in venous pressure. Threefoot, Gibbons, and Burch (1947) noticed a parallelism between changes in weight and changes in venous pressure when these were recorded daily over a period of many days, but were unable to find that either of these factors regularly preceded the other.

One would expect that a permanent escape of fluid from the intravascular to the extravascular compartment, caused by an increase in venous pressure, would produce haemoconcentration. But Merrill (1946) found just the opposite: several of his oedematous cardiac patients showed haemodilution. On the other hand, he produced evidence in favour of the suggestion made by Warren and Stead (1944), that the retention of salt and water in the body is of renal origin, by finding a diminished renal blood-flow and diminished glomerular filtration in all the subjects of chronic heart failure whom he investigated.

Mokotoff, Ross, and Leiter (1948) demonstrated that the rate at which sodium is reabsorbed in the tubules from the glomerular filtrate is identical in normal people and in patients with heart failure. Owing to diminished glomerular filtration, in heart failure most of the filtered sodium is reabsorbed and retained in the body.

The above evidence against Starling's theory was considerably weakened by Landis, Brown, Fauteux, and Wise (1946), who demonstrated that in dogs muscular exercise normally causes a fall of venous pressure, whereas in dogs with experimentally induced damage to the heart, though the resting venous

[1] Received September 28, 1949.

pressure remains normal, the same amount of exercise causes it to increase markedly. Consequently no definite conclusions as to the role of venous pressure in the genesis of cardiac oedema can be drawn from experiments and observations in which only the resting venous pressure has been recorded. Nor is it certain that the sequence 'diminished cardiac competence→increased venous pressure' is inevitable. On the basis of experimental evidence McMichael (1946) suggested that the increase in venous pressure may be due to an active venoconstriction which acts as a compensatory mechanism, since the venous system consists of contractile living vessels and not of inactive rigid tubes. Warren and Stead (1944) attributed the rise in venous pressure to an increased volume of plasma, and this in turn to the enhanced volume and pressure of extracellular fluid.

All the evidence mentioned above was based on static observations, the registered changes reflecting a new equilibrium but affording no evidence as to how it is brought about. A diminished renal blood-flow, for example, might be either the cause or the consequence of changes in the tissues. It seemed to us that only detailed haemodynamic observations made at the time when the water balance was changing could solve the problem. An attempt had been made by Stewart (1941) to discover whether haemodilution preceded the onset of diuresis in cardiac patients. He made his measurements only once a day, so that his data again were static, and reflected a new equilibrium without affording any information as to its genesis. The experiments of Burch, Reaser, and Cronvich (1947) showed that the equilibrium between blood and extracellular fluid is established very quickly, so that only repeated observations at short intervals can register the change. The disturbed water balance of cardiac patients is expressed in their low output of urine, and its changes are reflected in the spontaneous onset and decline of diuresis. Should we be able to register the detailed sequence of events in the course of this spontaneous change of urine flow, our problem might be solved. Such a change occurs in many cardiac patients at night, when their low output of urine increases to normal or even to a polyuria. Thus an investigation of the mechanism of nocturia seemed to be the best line of inquiry. Should Starling's theory be true, the sequence of events during the change from a low to a high flow of urine would be as follows: improved cardiac competence at night→fall of venous pressure→shift of fluid from the extravascular to the intravascular compartment→haemodilution→diuresis (Fig. 1). If on the other hand the newly conceived 'forward failure' theory, based on a diminished renal blood-flow, were correct, the changes in water balance would occur in the following order: increased renal blood-flow→increased urine output at the expense of water in the plasma→haemoconcentration→shift of fluid from the extravascular to the intravascular compartment (Fig. 2). Our experimental data seem to bear out the latter view.

Methods

We carried out our experiments in 35 subjects, 10 of whom (three male and seven female) were either normal or suffering from minor and insignificant

complaints, and could be considered as controls. Of the 25 patients with heart disease, six (two male and four female) had no evidence of heart failure, while in 19 (four male and 15 female) heart failure was present to a varying extent. The diagnoses are shown in the Table, which is a summary of all our data.

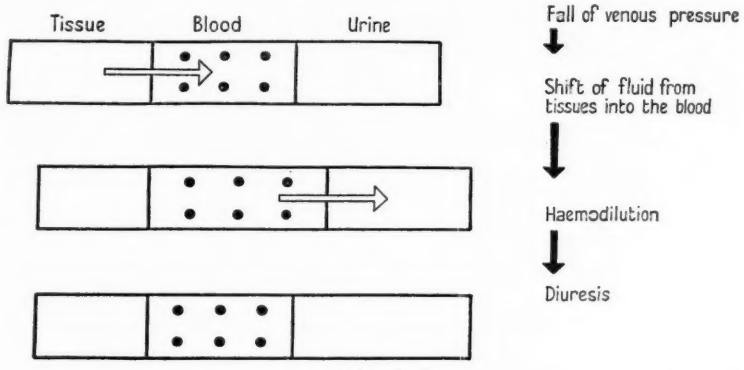

FIG. 1

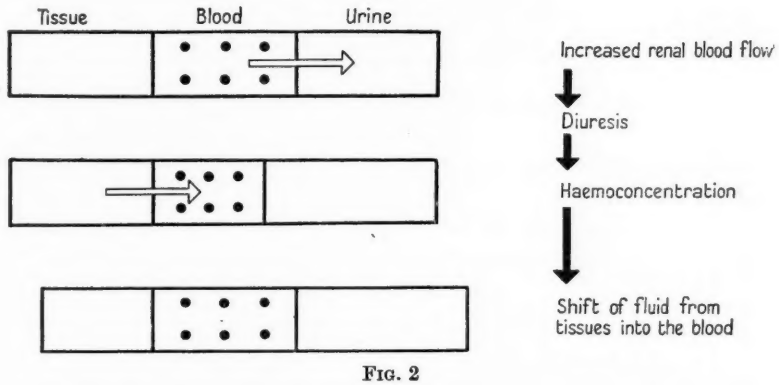

FIG. 2

FIGS. 1 and 2. Schematic representation of the mechanism of nocturia, assuming that cardiac oedema is due (Fig. 1) to venous congestion, or (Fig. 2) to diminished renal blood-flow.

All the patients were on a standard hospital diet for at least one week prior to the experiment. During this period their urine was collected at three-hourly intervals, so that some idea could be obtained of its variations in quantity. On some of these days sedatives were given, in order to ascertain that their use would not interfere with the variations of urine output. No cardiotonics or diuretics were administered to any of the patients prior to the experiment. Most of the patients were kept in bed during the whole preparatory period. On the day of the experiment all the conditions of the previous days were strictly adhered to. The experiment was planned in such a way that the expected change in diuresis would occur three to four hours after the first

TABLE

The Patients investigated, with Diagnoses and Data obtained as to Haemodynamic and Renal Functions

RHD, rheumatic heart disease; IHD, ischaemic heart disease; HHD, hypertensive heart disease; SHD, syphilitic heart disease; MR, mitral regurgitation; MS, mitral stenosis; AR, aortic regurgitation; AS, aortic stenosis; LF, left-sided failure; RF, right-sided failure. In columns *q*, *r*, *s*, the range of variations is recorded. The data in columns *g* to *p*, *t*, and *u*, are averages of several periods at a relatively constant urine flow.

Case number	*Sex*	*Age (years)*	*Body-surface area (sq. m.)*	*Diagnosis*	*Degree of heart failure*	*Urine flow (ml./min.)*	*Oxygen consumption (ml./min.) per sq. m. body-surface*	*A/v. oxygen difference (ml.%)*	*Oxygen saturation of art. blood (%)*	*Cardiac output (ml./min.) per sq. m. body-surface*	*Renal plasma-flow (CPAH) (ml./min.) per 1·73 sq. m. body-surface*	*Renal blood-flow*	*Renal fraction (%)*	*Glomerular filtration (Cinul. ml./min.) per 1·73 sq. m. body-surface*	*Filtration fraction (%)*	*Plasma-proteins (%)*	*Haematocrit (%)*	*Right auricular pressure (cm. water)*	*Circulating blood volume (ml. per sq. m. body-surface)*	*Vital capacity (ml.)*
a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*	*j*	*k*	*l*	*m*	*n*	*o*	*p*	*q*	*r*	*s*	*t*	*u*
1	F	28	1·56	Vegetative neurosis	0	0·51	146·5	2·52	97	5,820	634	1,100	9·25	117·0	18·4	7·90 to 8·78	40·6 to 44·75	+0·5 to +2·5	3,160	3,320
2	F	28	1·46	Mediastinal tumour	0	0·36	141·0	3·65	91·4	3,860	558	915	13·45	115·2	20·6	7·37 to 8·07	37·5 to 42·0	+0·5 to +5·5	2,720	3,050
3	F	18	1·54	Normal	0	0·78	150·0	4·25	..	3,530	542	906	14·85	106·2	22·1	7·90	40·25	+1·50 to +2	2,800	..
						0·43	165·5	3·00	96·0	5,530	670	1,113	11·60	95·2	14·2	7·36 to 7·90	35·4 to 38·5	+2 to +3·5	..	2,590
4	M	40	1·76	Convalescent from pneumonia	0	1·38	156·0	3·72	..	4,190	394	666	9·2	115·8	29·4	6·79 to 7·22	39·5 to 42·4	+1 to +8	2,065*	3,170
5	F	19	1·53	Normal	0	0·44	132·3	2·89	83·7	4,570	478	814	11·55	90·0	18·8	7·53 to 8·24	39·85 to 42·4	+0·5 to +2·0	2,140	2,790
6	M	37	1·78	Normal	0	1·02	163·5	4·92	90·0	3,330	1,080	2,060	38·5	148·0	13·7	7·14 to 7·53	47·3 to 49·0	−0·5 to +0·5	3,070	3,400
						0·55	164·5	3·49	90·0	4,700	804	1,535	19·8	98·6	12·15	6·97 to 7·53	47·3 to 48·7	−0·5	..	3,640
7	F	19	1·59	Normal	0	0·56	168·0	4·35	97·0	3,860	535	934	13·46	119·5	22·35	6·11 to 6·79	42·9 to 44·75	+0·5 to +3·5	..	2,515
						2·02	178·0	4·27	..	4,160	640	1,082	14·81	126·4	21·4	6·28 to 6·47	41·9 to 44·5	−1·5 to +0·5	..	2,750
						0·64	145·0	4·30	95·2	3,370	449	750	13·8	125·0	27·8	6·28	40·35 to 41·2	−0·5 to −2·5	..	2,600
8	F	18	1·45	Normal	0	0·61	..	..	..	..	578	866	..	130·0	22·5	6·79	38·5	..	..	..
						2·83	..	..	..	..	670	993	..	142·0	21·2	6·62 to 6·75	37·5 to 38·85	..	2,830	..
						0·74	..	..	..	..	826	1,190	..	115·5	14·0	6·28 to 6·62	36·0 to 38·1	..	..	..
9	M	29	1·87	Normal	0	2·08	158·8	3·31	91·7	4,770	904	1,435	15·61	96·2	10·63	6·75 to 7·00	37·2 to 38·5	−2·5 to +1·5	2,710	5,070
						0·56	124·5	2·88	..	4,330	1,157	1,850	24·08	88·0	7·52	6·62	36·5 to 37·5	−2·5 to −0·7	..	5,130
10	F	19	1·73	Normal	0	2·96	119·7	2·7	91·8	4,430	645	1,092	13·35	119·5	18·52	6·28 to 6·47	40·7 to 42·95	+7 to +8	2,890	3,385
						0·81	124·4	3·5	86·8	3,540	654	1,104	13·94	99·2	15·16	6·19 to 6·47	40·3 to 41·1	+4·5 to +8	..	3,430
11	F	36	1·57	RHD, MR	0	0·48	145·2	2·57	95	5,650	453	725	9·61	104·8	23·0	6·40 to 7·36	36·4 to 39·8	+4 to +7·5	3,720	2,470
12	F	19	1·53	RHD, MR	0	1·83	..	..	..	..	430	717	..	112·5	26·2	7·9 to 8·24	39·7 to 44·0	+14·5 to +16†	2,800	..
						0·59	..	..	..	..	465	755	..	105·5	22·7	7·53 to 7·90	37·9 to 38·8	..	..	..
13	F	27	1·56	RHD, MR	0	1·59	158·3	3·86	85·8	4,100	630	944	13·4	131·2	20·8	7·71 to 8·43	32·1 to 35·3	+1·5 to +4·5	..	2,780
14	F	33	1·39	RHD, MS, pulmonary infarction	±	0·90	201·5	4·25	94·0	4,740	298	..	..	92·0	30·5	7·37 to 8·07	..	+0·5 to +3	..	1,919

a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*	*j*	*k*	*l*	*m*	*n*	*o*	*p*	*q*	*r*	*s*	*t*	*u*
15	M	52	1·78	RHD, AR	±	0·82	189·1	3·71	83·4	5,110	446	732	8·33	117·0	26·15	7·14 to 8·34	38·5 to 41·0	+1 to +4·5	5,580	2,450
						1·29	196·5	4·76	84·9	4,130	585	962	13·17	138·2	22·8	7·36 to 7·53	38·0 to 39·4	+1	..	2,175
16	F	28	1·53	RHD, AR, AS, MS	+	0·65	182·0	4·63	84·6	3,920	661	1,070	..	132·5	20·0	5·93 to 6·27	37·3 to 39·95	+8	3,410	2,500
						1·27	180·0	3·27	88·5	4,800	760	1,220	13·0	164·0	21·6	6·1 to 6·27	37·35 to 37·8	+6	..	2,125
						0·46	147·6	2·5	84·4	5,900	700	1,120	11·33	132·0	18·85	5·74 to 5·93	36·6 to 38·6	+3·5 to +5·5	..	1,775
17	F	47	1·73	RHD, MS	++	0·53	140·3	5·29	92·5	2,660	279	488	10·77	98·0	35·1	7·53 to 7·9	41·6 to 43·7	+8 to +11·5	3,220	1,535
						0·83	150·3	4·70	95·9	3,210	474	836	17·0	137·5	29·0	7·37 to 7·90	42·25	+5 to +9	..	1,545
18	F	43	1·71	RHD, MS	++	0·84	146·8	4·03	89·0	3,640	421	725	11·71	104·5	27·3	7·14 to 8·24	41·1 to 44·0	+3·5 to +10	2,820	1,673
19	F	62	1·60	RHD, MS, HHD, RF, LF	+++	0·218	145·0	9·0	75·0	1,610	80	138	4·77	36·9	47·7	7·71 to 8·07	42·5 to 48·0	+12 to +18	2,280	1,200
20	F	45	1·60	SHD, AR, LF	+	0·87	168·0	2·10	90·2	8,000‡	316	548	3·95‡	65·3	20·55	7·15 to 7·7	42·25 to 43·0	+4·5	3,695	2,237
						1·34	142·0	4·92	90·5	2,880‡	783	1,365	27·4‡	115·5	14·8	7·0 to 7·15	42·0 to 42·5	+7·5	..	2,045
21	F	61	1·67	IHD, LF, RF	+	0·51	..	..	..	..	169	328	..	59·6	35·3	8·07	50·0 to 50·4	..	3,062	..
						1·26	..	..	..	..	233	456	..	65·7	28·2	8·14 to 8·25	50·5 to 51·0	..	..	..
						0·49	..	..	..	..	157	296	..	59·7	37·9	8·07 to 8·28	48·0 to 49·4	..	..	..
22	F	68	1·70	IHD, LF	++	0·47	..	5·1	81·4	..	150	212	..	53·0	35·2	7·07 to 7·14	28·8 to 29·4	+8·5 to +13·5	2,850	1,100
						3·13	102·3	3·65	70·7	2,810	233	331	6·48	62·0	26·6	7·07 to 8·07	27·4 to 31·4	+7 to +9	..	1,100
23	F	68	1·54	IHD, LF, RF	++	0·59	120·4	3·6	85·5	3,350	269	427	8·17	62·4	23·2	7·9 to 8·97	43·0 to 44·6	..	2,870	1,210
						1·22	120·9	3·9	..	3,330	351	559	11·01	66·8	21·2	7·72 to 7·9	44·25 to 45·3	..	..	1,130
24	F	64	1·52	IHD, RF	++	0·39	..	..	..	..	214	339	..	81·9	38·2	7·53 to 7·90	43·5 to 45·4	..	2,740	..
						0·77	..	..	..	..	315	489	..	103·7	32·8	7·14 to 7·53	42·5 to 44·5	..	..	..
						1·11	..	..	..	..	369	592	..	102·2	27·7	7·45 to 7·90	43·4 to 47·7	..	..	..
25	F	68	1·17	IHD, RF	+++	0·67	134·7	4·0	..	3,360	109	170	3·18	32·4	29·7	6·62 to 6·97	33·2 to 36·5	+1 to +10·5	3,280	667
26	F	64	1·53	IHD, LF	+++	0·42	161·3	5·22	72·4	3,100	180§	343	10·9§	75·0	41·7	7·05 to 7·62	44·1 to 48·7	+3·5 to +9	4,470	925
						0·91	157·9	4·74	71·1	3,340	231	408	6·87	80·0	34·6	6·88 to 7·5	42·6 to 44·0	+9 to +9·5	..	804
27	F	57	1·45	IHD, RF	+++	0·21	143	11·57	93·0	1,234‖	86	147	6·92	49·4	57·8	6·28	41·3	+36·5	4,450	650
						1·62	171	8·95	72·5	1,910	188	325	10·92	58·0	30·8	6·28	41·15 to 42·55	+24·5 to +29·5	..	850
						0·27	155·3	8·80	85·2	1,765	95	162	5·49	31·9	33·8	5·93 to 6·28	39·75 to 41·5	+27 to +29	..	750
28	M	51	1·84	HHD	0	0·73	123	3·10	90·5	3,970	203	357	5·18	68·0	33·4	7·05	42·7	+0·5	4,170	3,250
						2·81	173	3·95	85·5	4,370	468	828	11·34	117·0	25·0	7·00 to 7·05	42·7 to 43·2	0	..	2,933
						0·26	131	5·43	86·6	2,410	299	525	13·91	74·5	24·9	6·38 to 7·05	41·8 to 43·2	0 to −1·5	..	3,165
29	M	53	1·91	HHD, LF	++	4·28	172·5	5·54	77·0	3,100‖	254	452	8·38	62·2	24·5	6·79	43·7	+6	3,270	1,850
						1·51	172·5	4·12	75·0	4,180	141	238	3·44	35·4	25·1	6·47 to 6·88	40·5 to 43·4	+5·7 to +6·3	..	2,125
						0·55	165·0	4·43	82·8	3,590	76	128	2·07	24·4	32·05	6·47 to 6·87	39·5 to 41·4	+4 to +6·5	..	2,520
30	F	73	1·62	HHD, LF	++	0·81	123·0	4·85	90·5	2,540	179	308	6·9	59·5	33·2	6·53 to 6·97	..	+4·5 to +7	2,490	1,170
31	M	57	1·80	HHD, LF, RF	++++	0·39	144·8	7·08	82·2	2,400	77	158	4·44	37·5	48·2	6·29 to 7·37	47·6 to 51·0	+23·5 to +31	4,080	1,477
32	F	61	1·60	HHD, chronic bronchitis, emphysema, LF, RF	++	0·76	159·0	6·8	..	2,340	170	279	6·69	58·1	34·2	6·67 to 6·97	40·1 to 41·5	+13 to +19	4,070	1,485
						2·04	157·0	6·18	..	2,540	302	505	10·42	86·5	28·6	6·79 to 7·47	40·0 to 41·5	+11·5 to +15·5	..	1,400
33	F	68	1·52	HHD, bronchiectasis, LF, RF	++	0·65	139·5	3·95	90	3,540	288	480	7·54	60·1	21·5	7·35 to 8·25	38·5 to 40·7	+4·5 to +7·5	2,390	966
						1·18	129·5	3·88	95·0	3,330	306	502	8·11	70·3	23·0	7·53 to 8·61	38·5 to 38·6	+4·5 to +6·5	..	993
						0·76	123·5	4·26	95·2	2,910	238	392	8·10	65·4	26·9	7·14 to 7·90	39·3 to 42·1	+7	..	1,200
34	M	51	1·58	HHD, kyphoscoliosis, LF, RF	+++	2·61	187	3·52	58·9	5,310	304	528	5·31	38·0	12·54	5·7 to 5·9	40·92 to 40·95	+4·5 to +11	3,590	..
						0·91	181	2·56	61·2	7,080	205	362	3·31	34·4	17·0	6·1	42·3	+4·0	..	..
						0·42	177·5	5·71	..	3,180	126	217	2·95	36·0	28·6	5·56 to 6·1	40·1 to 44·1	+4 to +10·5	..	..
35	M	45	1·58	Pulmonary fibrosis, RF	++++	0·74	136	5·88	74·3	2,310	158	284	6·97	58·3	40·3	6·97 to 7·53	43·6 to 47·25	+23·5 to +26	3,290	970

* Unreliable; turbid plasma. † Venous pressure. ‡ Unreliable. § Unreliable; pulmonary oedema. ‖ Pulmonary oedema.

observations. After this change had occurred the experiment was continued for at least three hours. The total duration of the observations varied from five to twelve hours, which were divided into periods varying from 10 to 60 minutes, depending on the rate of urine flow. Usually the experiments were started in the afternoon or early evening, and were finished in the early hours of the next morning. They were carried out in a quiet side-room with a minimum of observers and of disturbance to the patients, who took dinner at the usual time in the course of the experiment. During the night the room was kept dark. Five patients, who were suffering from frequent attacks of pulmonary oedema, had an attack during the course of the experiment. A few complained of lassitude towards the end of the experiment, but most stood the investigation without any difficulty, and even slept quietly through the greater part of it. The data were discarded in cases where anxiety was a marked feature. The observations recorded therefore represent the usual physiological conditions of each patient.

The following investigations were made in each case. Cardiac output was estimated by the direct Fick method. Oxygen consumption was measured with the Krogh spirometer, which gave consistent results. The Roughton–Scholander (1943; Fejfar and Brod, 1948) micromethod was used for the determination of the oxygen content of the arterial and mixed venous blood. Venous blood was obtained from the right auricle through a cardiac catheter, the position of which was controlled by X-rays. It was left in position throughout the experiment without causing any complications. Right auricular pressure was measured with a water-manometer and referred to the phlebostatic level (Winsor and Burch, 1946). Normally it rarely exceeded +3 cm. of water. Renal plasma-flow (clearance of *p*-aminohippuric acid, PAH) and the rate of glomerular filtration (inulin clearance) were estimated by the usual clearance technique described in detail by Goldring and Chasis (1944). The sustaining solution of inulin and PAH was infused by a pressure-pump connected with the cardiac catheter, at a constant rate of 0·2 ml. per minute. This slow speed (12 ml. per hour) could not interfere with the water balance of the patient. Clotting was prevented by the pressure in the system and by the addition of one ml. of heparin to 100 ml. of the infused solution. *P*-aminohippuric acid was estimated by the method of Smith, Finkelstein, Aliminosa, Crawford, and Graber (1945), and inulin by that of Harrison (1942). Variations of less than 10 per cent. in the inulin clearance and of less than 20 per cent. in the PAH clearance were considered insignificant. The filtration fraction was expressed by the ratio $\frac{C_{inul.}}{C_{PAH}} \times 100$; its normal value is 18·8±4·3 per cent. (Brod, 1949). The rate of tubular reabsorption of water was assessed from the inulin concentration index (inulin U/P ratio). The renal fraction of the cardiac output ($\frac{\text{renal blood-flow}}{\text{cardiac output}} \times 100$) ranges normally from 15 to 25 per cent. Renal blood-flow was calculated from the PAH clearance and the corresponding haematocrit reading. The corresponding value of the cardiac output was found by inter-

polation, the intervals between adjacent estimations being made as short as possible. The changes in the water-content of the plasma were assessed from the changes in percentage of plasma-proteins (estimated by the copper-sulphate method of Phillips, Dole, Hamilton, Emerson, Archibald, and Van Slyke, 1945–6), from haematocrit readings, and from the disappearance curve of Evans's blue (T 1824; Evans and Gibson, 1937). Vital capacity was measured at least in duplicate at the end of every breathing period of 10 minutes with Krogh's spirometer.

Typical Results

A typical experiment carried out in a normal man of 37 years is presented in Fig. 3. The urine flow was above one ml. per minute throughout the day. At 20.30 hours it started to decline, and fell soon afterwards to the level of 0·5 ml. per minute at which it remained until the end of the experiment at midnight. This fall in diuresis ran parallel to a fall in the rate of glomerular filtration ($C_{Inul.}$) from 135 to 180 ml. per minute during the day to less than 100 ml. per minute at night. At the same time the inulin U/P ratio increased, pointing to an increase in the tubular reabsorption of water. Renal plasma-flow (C_{PAH}) changed similarly, falling from a very high level of over 1,000 ml. per minute during the day to 700 ml. per minute at night. It decreased, however, later than the glomerular filtration and to a lesser degree. Consequently the filtration fraction gradually fell from 17·1 to 10·5 per cent. The fall in renal blood-flow was not due to any parallel change in the cardiac output which, on the contrary, rose at night from 5·5 to 8·5 litres per minute, with a consequent fall of the renal fraction from 37 to 15·9 per cent. The right auricular pressure was within normal limits throughout the experiment; it decreased slightly during the decline of diuresis. Plasma-proteins, haematocrit values, and the disappearance curve of T 1824 ran exactly parallel in this subject, and although the changes were slight, their agreement must be considered significant. There was an obvious decrease in all these three values in the late hours of the afternoon, shortly after the urine flow fell from two to one ml. per minute, suggesting that haemodilution had occurred. After this they increased slightly, but with the nocturnal fall in diuresis there was a further haemodilution lasting until 22.30 hours, when the three values returned to the level at which they stood late in the afternoon. Vital capacity increased insignificantly at night.

To sum up: the nocturnal decline of urine flow in this normal subject was due both to a decrease in the rate of glomerular filtration and to a simultaneous increase in the tubular reabsorption of water. These changes were independent of the behaviour of the renal blood-flow, and they were accompanied or followed by haemodilution, which did not provoke any new increase in urine flow. Similar behaviour was encountered in the remaining normal controls.

In patients with heart disease the results of individual experiments were less consistent. But an evaluation of the accumulated data revealed uniform features.

As an example the results in three patients are presented in detail. Fig. 4 presents the experimental data in a woman of 57 years who had ischaemic heart disease and severe congestive heart failure. She had oliguria (about 0·1 ml. per minute) during the day. At 21 hours her urine flow suddenly rose to two ml. per minute. It decreased slightly after one hour, but a satisfactory diuresis of

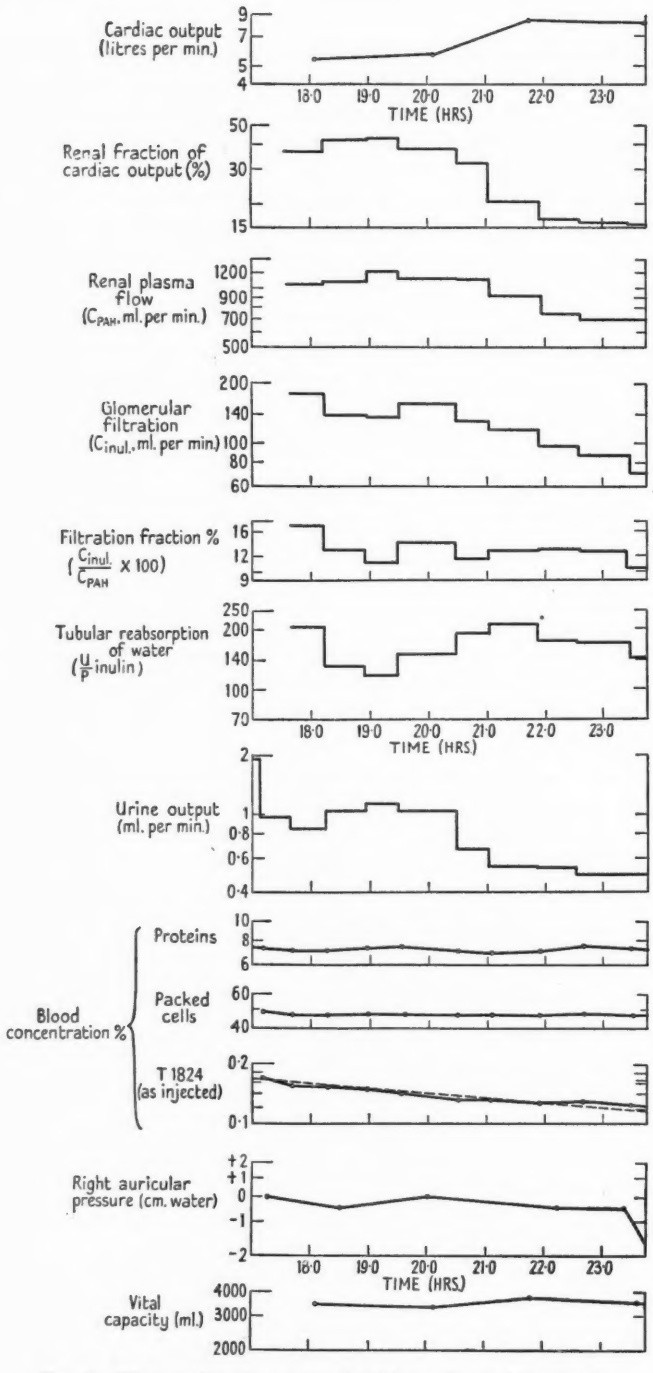

FIG. 3. Observations in a normal subject. *See text for details.*

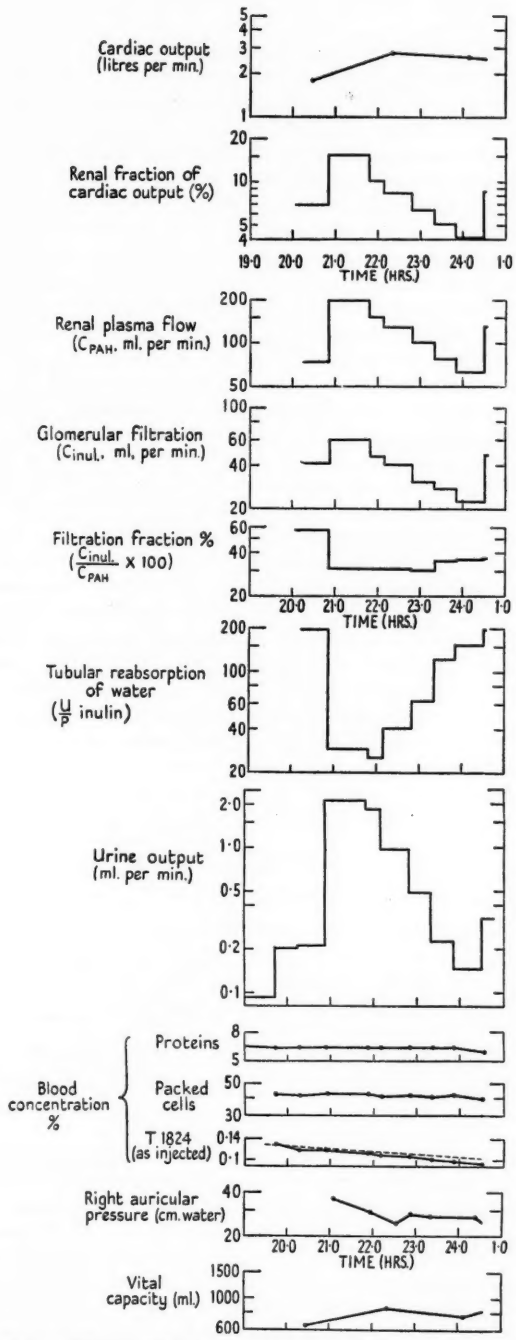

Fig. 4. Observations in a patient with ischaemic heart disease and heart failure. *See text for details.*

more than one ml. per minute was maintained until 23 hours, when the urine flow fell rapidly to its midnight level of 0·15 ml. per minute. The fluctuations in diuresis were closely paralleled by changes in glomerular filtration. At the peak of diuresis, however, the rate of glomerular filtration did not exceed 60 ml. per minute, and it fell almost to one-third of this value when the urine flow became low. The changes in glomerular filtration were only partly responsible for the fluctuation of the urine flow, for the tubular reabsorption of water varied markedly at the same time, the inulin U/P ratio decreasing from 196·5 to 29 at the peak of diuresis. This ratio rose again to 154·5 per cent. when the diuresis declined. Contrary to their behaviour in normal subjects, the changes in the rate of glomerular filtration ran parallel to the renal plasma-flow, which increased to 195 ml. per minute when the urine flow was high and fell to the low level of 63 ml. per minute when the diuresis dropped. This change in PAH clearance was of a higher order of magnitude than the change in glomerular filtration. Consequently the filtration fraction decreased during the period of high urine output, and increased when the output was low. The cardiac output of this highly decompensated patient was very low, varying between 1·9 and 2·75 litres per minute. The changes in renal plasma-flow did not run parallel to the changes in cardiac output, for the latter reached its peak when the urine flow and the inulin and PAH clearances were falling steeply. Consequently the renal fraction of the cardiac output increased when the output of urine was high and fell when it became low. The right auricular pressure was very high throughout the course of the experiment, but dropped significantly (from 36 to 25 cm. of water) when the diuresis started to decline, and remained slightly above the latter level during the period of low urine flow. Plasma-proteins, haematocrit values, and the disappearance curve of T 1824 again ran roughly parallel in this patient. Their changes pointed to a very slight haemodilution during the early diuretic phase, but to a much higher one soon after the urine flow started to decline. Vital capacity was very low (640 ml.) at the beginning, when the patient complained of a dry cough; it increased to 820 ml. when the urine flow was high, and started to decline again when the diuresis fell.

In conclusion, we can say that in this severely decompensated cardiac patient the changes in urine flow were parallel to changes in the rate of glomerular filtration, which in its turn ran parallel to the more pronounced changes of renal blood-flow. The filtration fraction, which was high when the urine flow was low, decreased with the increase of renal blood-flow and of diuresis. The changes in renal function did not reflect changes of general haemodynamics. Very slight haemodilution occurred during the increase in diuresis, but a much more pronounced haemodilution later in the experiment was not followed by an increase in the urine output.

A different type of result is presented in Fig. 5. The patient was a woman of 61 years suffering from hypertensive heart disease, chronic bronchitis with emphysema of the lungs, and right-sided heart failure. Her urine flow was about 0·6 to 0·8 ml. per minute until late in the evening. At 23.30 hours it started to rise, and in the early hours of the morning amounted to 2·78 ml. per minute. As in the previous patient, this increase was closely parallel to an increase in the rate of glomerular filtration (from 49 to 90 ml. per minute), which again is inadequate to account for the total diuretic change. A fall in the inulin U/P ratio from 81 to 27·2 demonstrates that at least three-quarters of that change was due to a diminished tubular reabsorption of water. The increase in glomerular

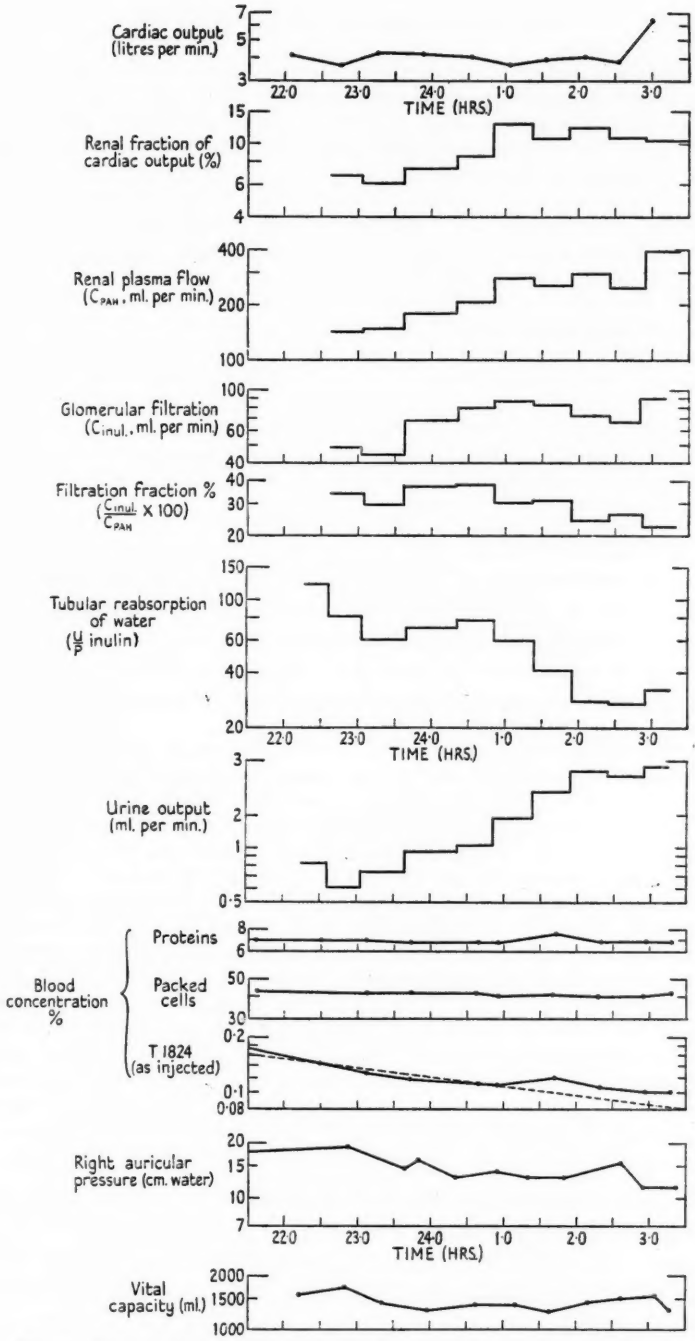

FIG. 5. Observations in a patient with hypertensive heart disease and very severe congestive heart failure.
See text for details.

filtration closely reflected the changes in renal plasma-flow (from 142 to 390 ml. per minute), and here again the variations of the latter were of a higher order, so that during the rise of diuresis the filtration fraction fell from 34 to 22·8 per cent. These changes of renal haemodynamics were again quite independent of variations in the cardiac output, if we except the last hour of the experiment. Cardiac output was moderately low and remained nearly constant most of the time, so that there was a marked rise in the renal fraction from the very low figure of 6·7 per cent. to 12·8 per cent. when the urine flow increased. Right auricular pressure was abnormally high throughout, but declined slightly and gradually with the onset of diuresis. Plasma-proteins, haematocrit values, and the T 1824 disappearance curve once more ran parallel so that their changes, although slight, must be considered to reflect shifts of the water in the plasma. There was a very slight decrease in the plasma-protein content and in the T 1824 concentration at 23.30 hours. This change was not accompanied by any fall in the haematocrit value. With the rising diuresis between 1 and 2 a.m. all three methods registered a marked transient haemoconcentration. Vital capacity was low throughout the experiment, and decreased at night.

In conclusion, this patient showed a marked nocturia, which was brought about by a significant increase in glomerular filtration and by a restriction of the tubular reabsorption of water. These changes occurred simultaneously with an increase in the renal blood-flow, which was not due to any change in the cardiac output. The right auricular pressure decreased from the moment of the onset of diuresis. At the same time a slight haemodilution was observed; a marked haemoconcentration occurred later when diuresis was high.

Fig. 6 summarizes our observations in a man aged 57 years, suffering from hypertensive heart disease and severe congestive heart failure with marked oedema. During the days preceding our main observation this patient had a very low urine flow, which showed no difference between day and night. On the day of the observation it was between 0·3 and 0·5 ml. per minute and did not change during the experiment. As might be expected, the rate of glomerular filtration was very low (33 to 45 ml. per minute), and its fluctuations were insignificant. The same was true of the renal plasma-flow, which showed slight variations around the value of 80 ml. per minute. The filtration fraction was abnormally high and fluctuated, except during the first period of urine collection, between 40 and 50 per cent. The cardiac output was below the range observed in most of our subjects, and varied insignificantly around 3·7 litres per minute. Right auricular pressure was very high (+25 cm. of water) and its variations insignificant. Plasma-protein, haematocrit, and T 1824 values varied concordantly, and pointed to a marked haemodilution in the early part of the night. This tendency to haemodilution was obvious throughout the experiment. Vital capacity in this patient was very low, and fell slightly during the night.

In conclusion, this patient who suffered from severe congestive heart failure had a fixed oedema, and an oliguria which showed no tendency towards improvement. His renal blood-flow and rate of glomerular filtration were very low, and the tubular reabsorption of water high. A marked haemodilution occurred at night.

Evaluation of Data

The above observations are representative of the various types of behaviour

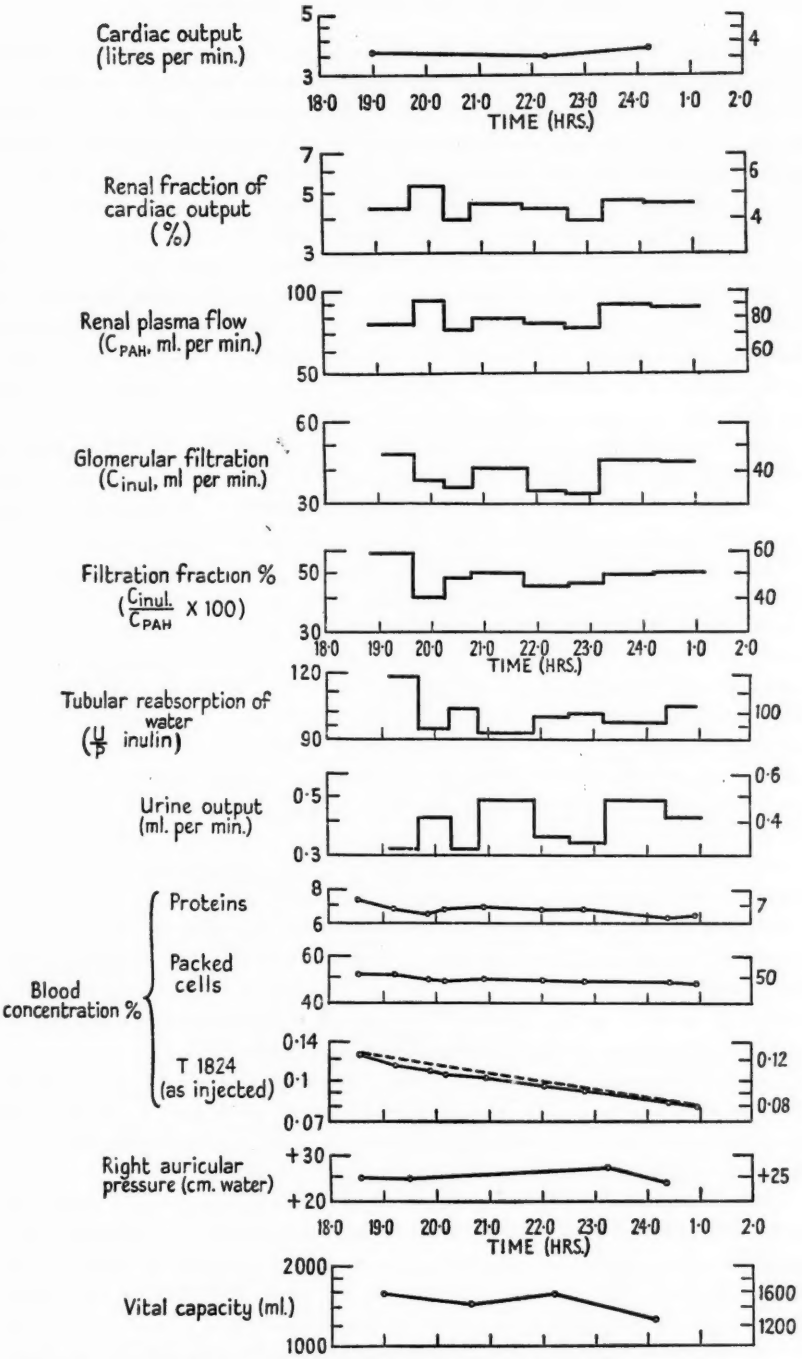

FIG. 6. Observations in a patient with hypertensive heart disease and a very severe congestive heart failure. *See text for details.*

encountered. The results of individual experiments, although allowing definite conclusions to be drawn, are not adequate to solve the whole problem. A solution is possible only by computing the data collected from all our experiments. For this purpose our patients have been divided into normal subjects and patients with evident heart disease, and the latter have been further subdivided into those without signs of heart failure and those with failure. In all three groups the patients fall into three sub-groups: (1) those whose urine flow increased at night by more than 0·5 ml. per minute; (2) those whose urine flow decreased at night by more than 0·5 ml. per minute; (3) those in whom the difference between the day and night urine flow was less than 0·5 ml. per minute. The moment of the change of urine flow was taken as zero hour. In sub-group 3 it was necessary to fix zero hour arbitrarily; 7 p.m. was chosen by analogy with the majority of patients in the other sub-groups.

Right auricular pressure (Fig. 7). A significant fall in right auricular pressure occurred in the majority of our subjects shortly after the beginning of the observation, irrespective of their subsequent behaviour. In normal subjects, a nocturnal change of urine flow was not preceded by any change in the composite r.a.p. curve. A slight rise of this curve followed a nocturnal fall in diuresis, as opposed to the slight fall of right auricular pressure in the one subject with nocturia. In compensated cardiac patients, changes in right auricular pressure were unrelated to changes in the output of urine. In decompensated cardiac patients whose urine flow diminished at night, the right auricular pressure behaved as it did in normal subjects, except that its nocturnal increase did not start until about an hour and a half after the fall in urine flow. A very marked initial fall, without any concomitant change in urine flow, occurred early in the experiment in cardiac patients with nocturia. Afterwards, while they still had oliguria, there was a slight increase in right auricular pressure of the same degree and shape as in the normal sub-group 3, where the urine flow was low and did not change. Some 30 minutes before the onset of nocturia the composite r.a.p. curve dropped by 1·5 cm. of water, and this drop continued for three hours after diuresis began. But it was of a much smaller degree than the initial fall, which was not followed by any change in urine flow. Moreover, it must be pointed out that the right auricular pressure did not behave uniformly in all the subjects of any sub-group.

It may be therefore concluded that the composite curves, whether in normal or in cardiac subjects, are not truly representative of the behaviour of the whole sub-group, and that no consistent change in right auricular pressure before the onset of diuresis could be observed in any sub-group.

Plasma-proteins (Fig. 8). In normal subjects of sub-group 2, the individual curves from which the composite curve is constructed were homogeneous. The composite curve begins to fall gradually and slightly several hours before the decline in urine flow, and shows a similar fall after that decline has begun. The average difference of the final from the initial protein concentration was −6 per cent. A very slight tendency to nocturnal haemodilution was noted also in two patients (sub-group 3) whose urine output did not change between

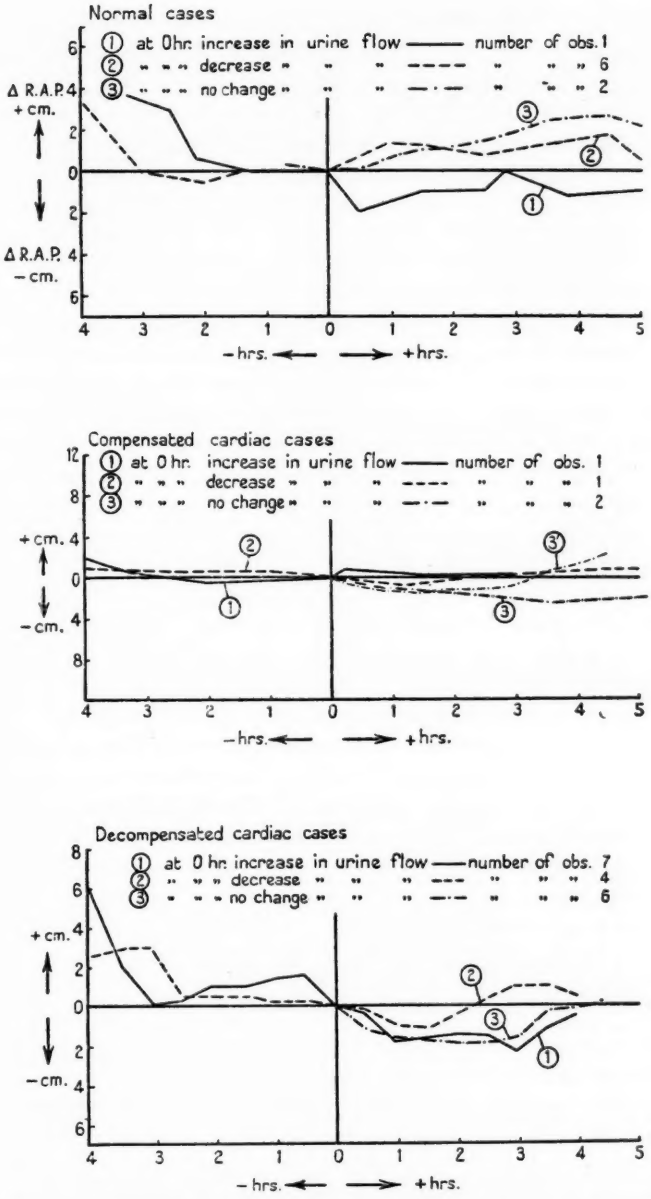
Normal cases
① at 0hr. increase in urine flow —— number of obs. 1
② " " " decrease " " " ---- " " " 6
③ " " " no change " " " —·— " " " 2
Δ R.A.P. + cm.
Δ R.A.P. − cm.
6 4 2 0 2 4 6
4 3 2 1 0 1 2 3 4 5
− hrs. ← → + hrs.
Compensated cardiac cases
① at 0 hr. increase in urine flow —— number of obs. 1
② " " " decrease " " " ---- " " " 1
③ " " " no change " " " —·— " " " 2
12 8 + cm. 4 0 − cm. 4 8
4 3 2 1 0 1 2 3 4 5
− hrs. ← → + hrs.
Decompensated cardiac cases
① at 0 hr. increase in urine flow —— number of obs. 7
② " " " decrease " " " ---- " " " 4
③ " " " no change " " " —·— " " " 6
8 6 + cm. 4 2 0 2 − cm. 4 6
4 3 2 1 0 1 2 3 4 5
− hrs. ← → + hrs.

FIG. 7. Composite diagrams showing absolute changes of right auricular pressure related to the change in urine flow, in normal and in cardiac patients. 0 hrs. represents time at which urine flow changed; Δ R.A.P. represents deviation of right auricular pressure, in cm. H_2O, from its value at 0 hrs. In patients with no change of diuresis, 0 hrs. was fixed arbitrarily at 7 p.m. (19 hrs.)

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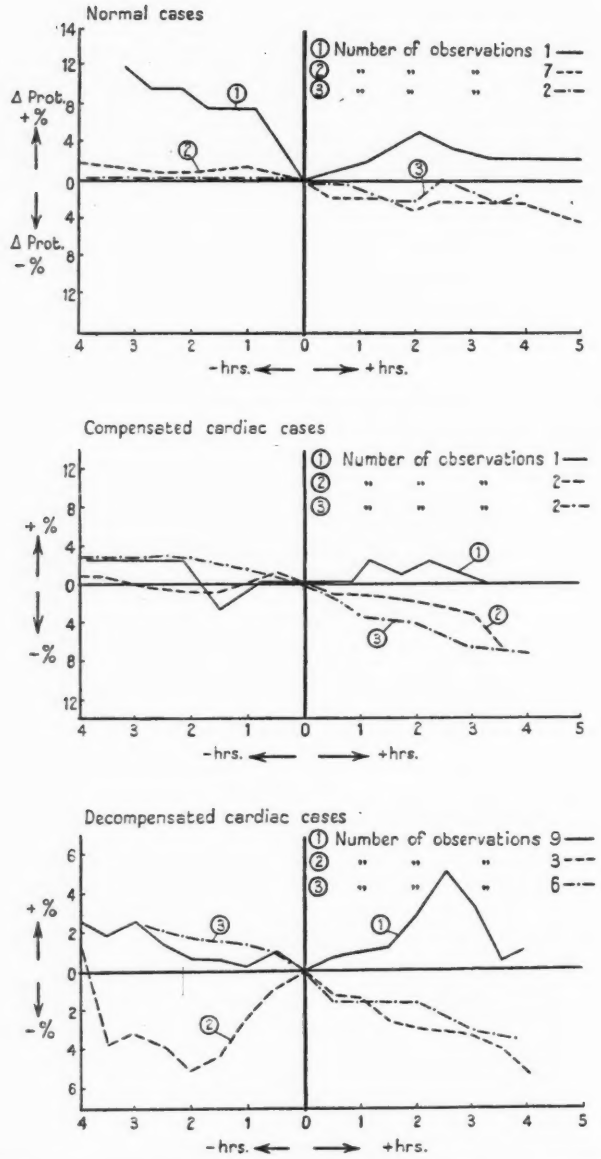

FIG. 8. Composite diagrams showing percentage changes of the plasma-protein content related to the change in urine flow at 0 hrs. In patients with no change of diuresis, 0 hrs. was fixed arbitrarily at 7 p.m. (19 hrs.). Δ (Prot.) % = deviation of plasma-proteins from their value at 0 hrs. The lines are classed as in Fig. 7.

day and night. But in the one normal subject whose urine output increased at night (sub-group 1) a marked haemodilution occurred about 50 minutes before the onset of diuresis, his plasma-protein concentration falling in this short space of time by 7·5 per cent. of its original value. After the diuresis had started there was a gradual increase in the plasma-protein concentration, but its peak two hours later was 2·5 per cent. below the initial level. From this moment onwards it showed a slight gradual fall. If a connecting line is drawn between the points of the curve at −50 minutes and at +2 hours, we get a protein concentration curve which is not markedly different from that of other subjects whose diuretic rhythm was normal. Exactly the same behaviour was observed in compensated cardiac patients.

Of the decompensated cardiac patients, three (sub-group 2) showed a marked decrease in plasma-protein concentration between the fourth and second hour before zero. During that time their urine output was normal or high. From −2 to 0 hours the protein concentration increased, and from 0 hours it assumed a gradual descending course, similar to but steeper than that observed in normal subjects of sub-group 2. This second part of the curve is exactly parallel to the average protein concentration curve of the six decompensated cardiac patients of sub-group 3, whose urine output was low by day and by night; but in the latter sub-group the decrease in concentration had already begun three hours prior to our arbitrary zero. If we connect the initial point of the curve for sub-group 2 with its point at 0 hours, we get a curve identical with that of sub-group 3; the actual curves differ only in a marked decrease of protein concentration in sub-group 2 early in the evening, when the urine flow was normal or high. In nine patients with nocturia (sub-group 1) the average protein concentration curve runs parallel in its first half to that of sub-group 3 and to the imaginary connecting line described for sub-group 2. But immediately after the increase in urine output it takes a very different course: the concentration rises, and two and a half hours after the onset of diuresis it has increased by 5 per cent. From this moment the curve begins to fall, but even four hours later it does not reach the expected point to which it would have fallen had it conformed to that of the other sub-groups. The composite protein curves are in every case representative of the behaviour of all the individuals in the sub-group and are, therefore, statistically significant.

Haematocrit (Fig. 9). In describing individual experiments we have already pointed out the close conformity between haematocrit and plasma-protein changes, although very often the former were less pronounced. The composite curves in normal subjects and in 17 patients with heart failure confirm this observation. They are similar both qualitatively and quantitatively to the protein curves, and need not be discussed separately. Owing to possible inaccuracies arising from technique, we were able to follow haematocrit changes in only four of our six compensated cardiac patients. These changes showed a similar trend to that of the other two groups, but in view of the paucity of our data we have not presented them in composite form.

T 1824 disappearance curves. The curves representing the disappearance of

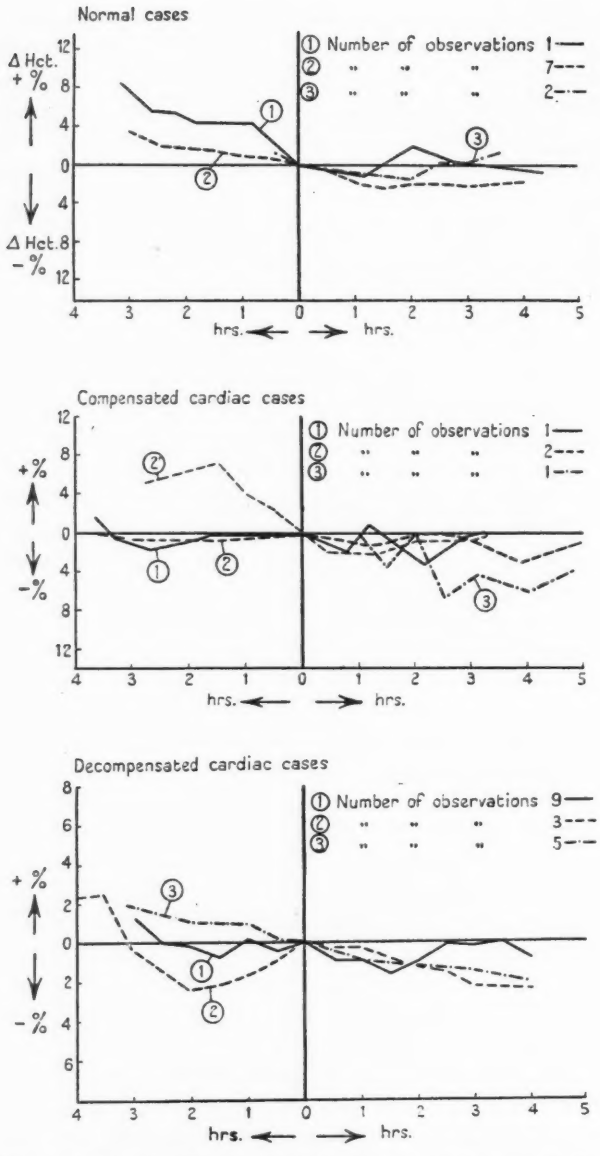

FIG. 9. Composite diagrams showing percentage changes of the haematocrit value (Δ Hct. %) from its level at 0 hrs., i.e. the time at which urine flow changed, in normal and in cardiac subjects. In patients with no change of diuresis, 0 hrs. was fixed arbitrarily at 7 p.m. (19 hrs.). In compensated cardiac patients, reliable data were obtained in only four cases, which are therefore presented individually. The lines are classed as in Fig. 7.

Evans's blue (T 1824) from the plasma were similar to those of the plasma-proteins and haematocrit. We abstain from presenting these data in composite form because some of the samples of plasma showed a lipaemic turbidity which we were unable to remove.

Renal plasma-flow (Fig. 10). In our normal subjects of sub-groups 2 and 3, no significant changes in PAH clearance (over ± 20 per cent. of the initial value) were observed at 0 hours. This agrees with the observations in a normal subject (Case 6) presented above in Fig. 3. The one patient whose urine flow increased at night exhibited a marked increase in PAH clearance before, and a gradual decline after, the onset of diuresis.

Of the decompensated cardiac patients, there were seven in whom the urine flow was normal or high at the beginning of the experiment (sub-group 2), and these all showed a marked decrease in PAH clearance (45 per cent.) some 60 minutes before zero. This fall continued steadily throughout the four hours following the diminution of urine flow, so that at the end of the observation the average clearance was 48 per cent. below its value at 0 hours. An exactly opposite change was observed in all the 11 cardiac patients with nocturia: there was a steep increase in renal plasma-flow beginning one hour before nocturia and continuing steadily for the next three and a half hours, the rise in PAH clearance from 0 hours amounting to 65 per cent. In the six decompensated subjects of sub-group 3 there was a slight gradual increase in PAH clearance during the course of the experiment, but even at the end of the observation period the total change did not exceed 20 per cent. of its original value. Similar behaviour was encountered among the six compensated cardiac patients, the only exception being that the nocturnal increase of PAH clearance among the subjects of sub-group 3 was significant.

Renal plasma-flow and right auricular pressure (Fig. 11). The importance of the fluctuations of renal plasma-flow in relation to changes of urine flow in cardiac patients is borne out by the data just presented. It was therefore important from the point of view of our problem to find whether there was a correlation between these changes and the variations of right auricular pressure. A glance at Fig. 11 will show that no such relationship exists in normal subjects. In decompensated cardiac patients the average r.a.p. curve fell slightly just before the flow of plasma through the kidney increased. A similar fall, however, occurred in patients whose renal plasma-flow either declined or did not change at 0 hours. Moreover, a much steeper fall in right auricular pressure at $-2\frac{1}{2}$ hours had no effect on the PAH clearance. It must also be remembered that the average r.a.p. curves are not representative of the behaviour of individual right auricular pressures in any of the sub-groups. We must conclude that there was no direct relationship between right auricular pressure and renal plasma-flow.

Renal blood-flow and cardiac output (Fig. 12). The next step was to find whether any relationship existed between the changes in renal blood-flow and those which occurred in cardiac output. In Fig. 12 the maximum deflections of renal blood-flow are plotted as percentage changes, against percentage changes of the

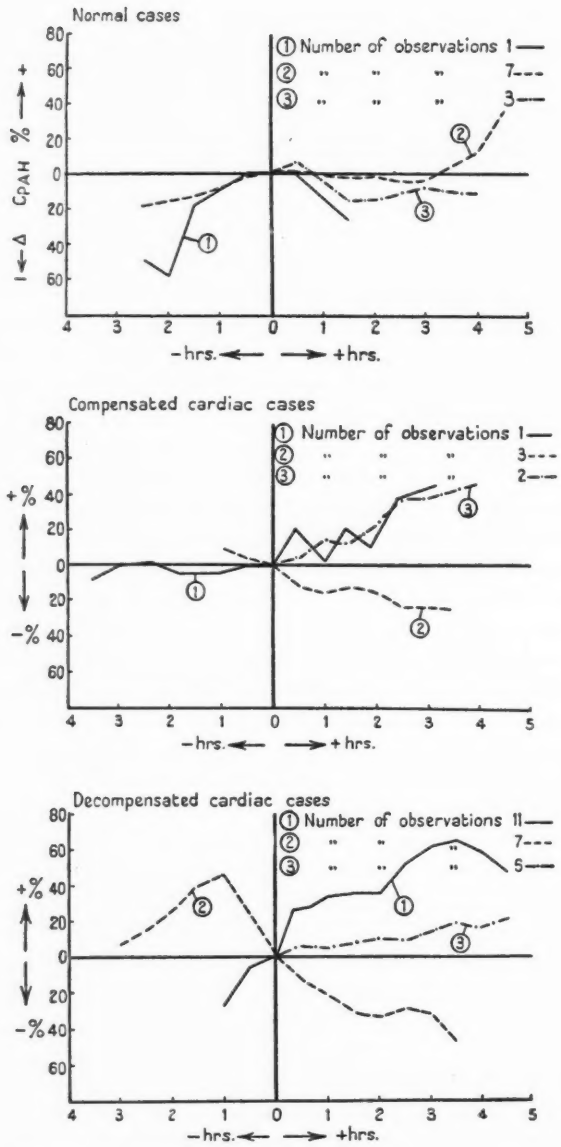
Normal cases
① Number of observations 1
② " " " 7
③ " " " 3
+ Δ C_{PAH} % −
80 60 40 20 0 20 40 60
4 3 2 1 0 1 2 3 4 5
−hrs. ← → +hrs.
Compensated cardiac cases
① Number of observations 1
② " " " 3
③ " " " 2
+% −%
80 60 40 20 0 20 40 60
4 3 2 1 0 1 2 3 4 5
−hrs. ← → +hrs.
Decompensated cardiac cases
① Number of observations 11
② " " " 7
③ " " " 5
+% −%
80 60 40 20 0 20 40 60
4 3 2 1 0 1 2 3 4 5
−hrs. ← → +hrs.

FIG. 10. Composite diagrams showing percentage changes (Δ %) of renal plasma-flow (C_{PAH}) from its level at 0 hrs. (time at which the urine flow changed) in normal and in cardiac subjects. In patients with no change of diuresis, 0 hrs. was fixed arbitrarily at 7 p.m. (19 hrs.). The lines are classed as in Fig. 7.

cardiac output at corresponding times. Should a correlation exist, the points would be situated along a line halving the right upper and left lower quadrants.

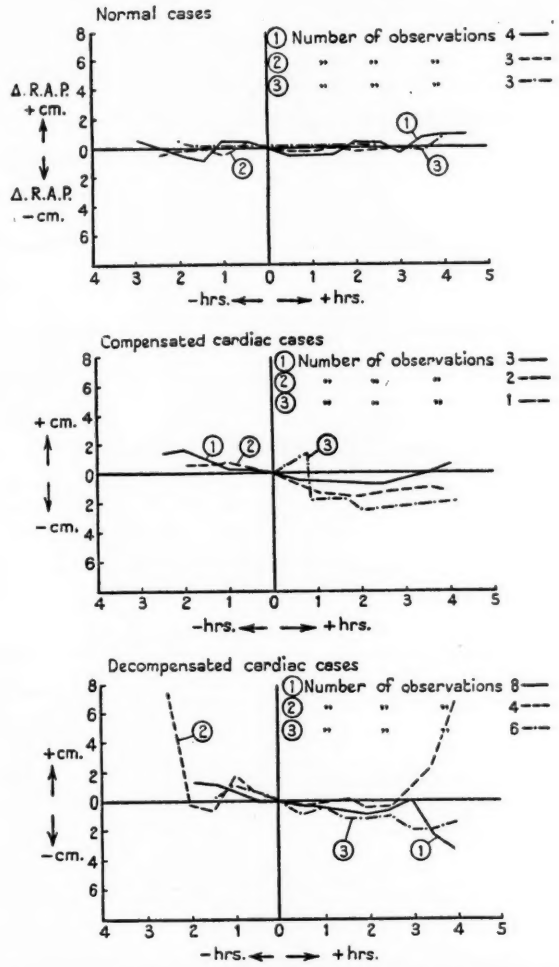

FIG. 11. Composite diagrams showing absolute changes of right auricular pressure in cm. H_2O (Δ R.A.P.) from its level at 0 hrs., when a change occurred in the renal plasma-flow, in normal and in cardiac subjects. In patients in whom there was no change in renal plasma-flow, 0 hrs. was fixed arbitrarily at 7 p.m. (19 hrs.). The lines are classed as in Fig. 7.

The two dotted lines are the ±20 per cent. deflection which has been allowed as the limit of error in the method employed. It can easily be seen that in one half both of normal and of cardiac subjects no such correlation existed. The results in five normal and nine cardiac patients were within this limit, while in six normal and eight cardiac patients great variations of renal blood-flow were

accompanied either by no significant change in cardiac output, or by changes which were disproportionately smaller. In one normal and three cardiac

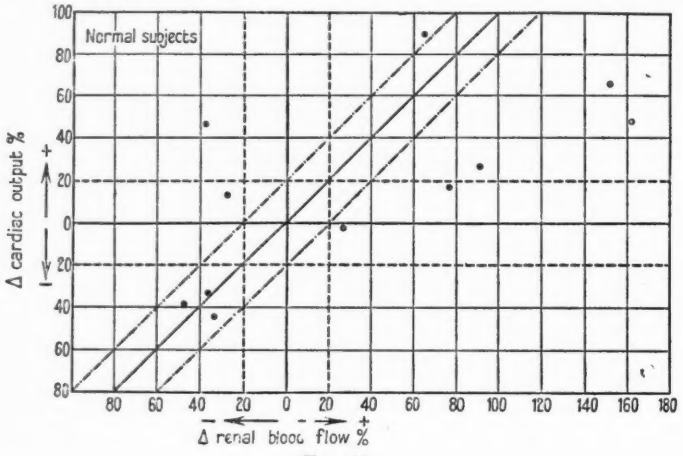

FIG. 12*a*

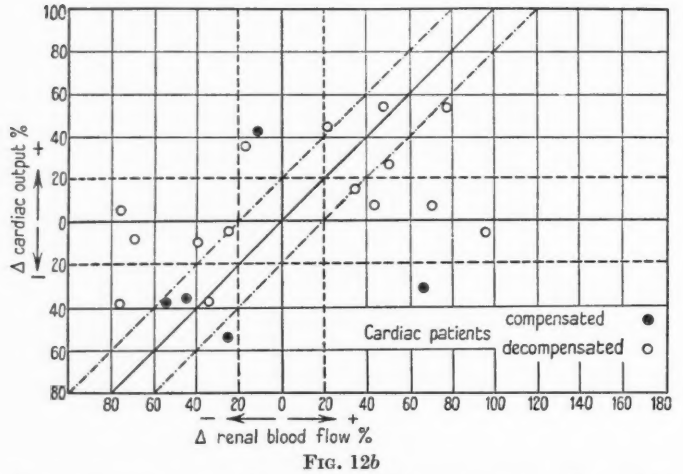

FIG. 12*b*

FIG. 12. Changes of renal blood-flow related to changes of cardiac output (*a*) in normal subjects and (*b*) in cardiac patients. Δ renal blood-flow = extreme percentage change (+ or −) in renal blood-flow observed in an individual patient. Where + and − changes both occurred in the course of the experiment, each of these changes is represented by a separate dot. Δ cardiac output = percentage change (+ or −) in cardiac output at the corresponding times. Should a direct relationship exist, the points would be situated along the diagonal halving the left lower and right upper quadrants. The dotted lines on both sides of ordinate, abscissa, and diagonal are the limits of error in the method employed.

patients the cardiac output changed more than the renal blood-flow. In one cardiac patient an increase of renal blood-flow by some 67 per cent. was accompanied by a 30 per cent. drop in the cardiac output. The data suggest that there

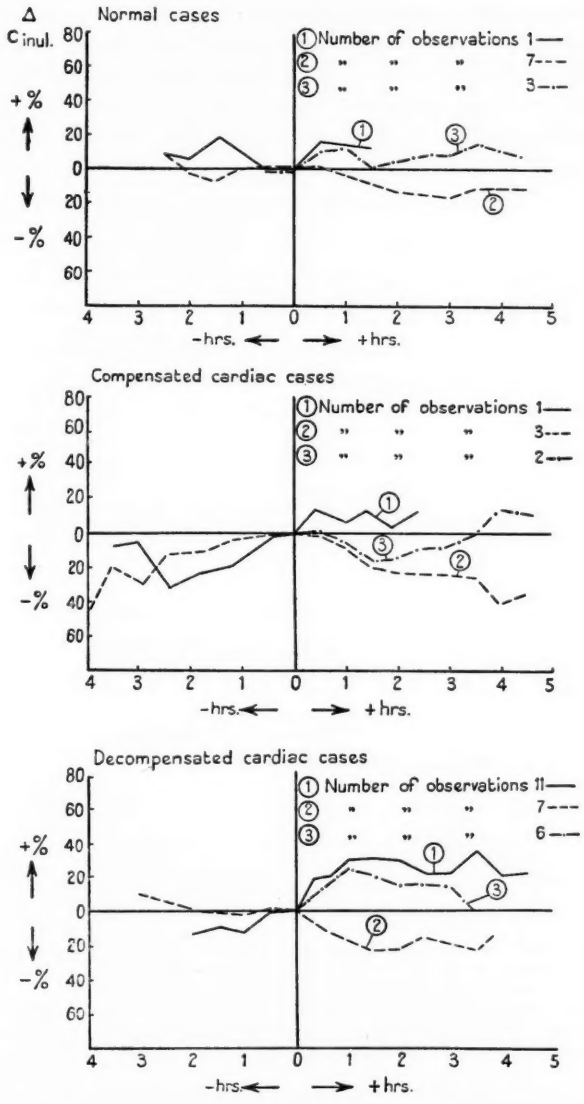

Fig. 13. Composite diagrams showing percentage changes in the rate of glomerular filtration (Δ $C_{inul.}$ %) related to 0 hrs., the time at which urine flow changed, in normal and in cardiac subjects. In patients with no change of diuresis, 0 hrs. was fixed arbitrarily at 7 p.m. (19 hrs.).

Urine flow at 0 hrs. { ① increased ——
② decreased ------
③ unchanged —·—

was no direct correlation between changes of cardiac output and changes in renal blood-flow.

Glomerular filtration (Fig. 13). As might be expected from the data of the

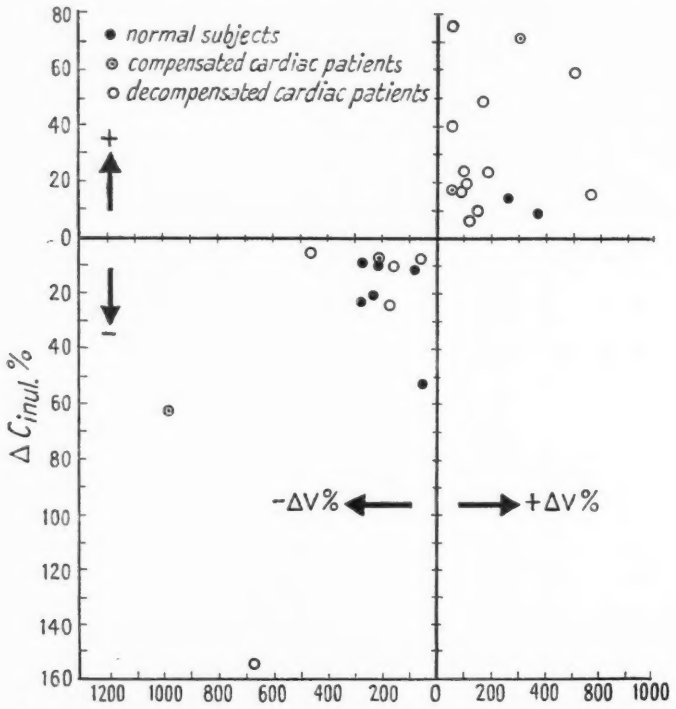

FIG. 14. Changes of urine flow (Δ V %) in relation to changes in the rate of glomerular filtration (Δ $C_{inul.}$ %) in normal and in cardiac subjects. The change, irrespective of its direction, is expressed in each case as a percentage of the lower value, in order to make the percentage conform to the absolute change. E.g. an increase of urine flow from 0·1 to 1·0 ml. per minute is a change of +900%; but a decrease of urine flow from 1·0 to 0·1 ml. per minute, if expressed as a percentage of the original value, would be a change of only −90%.

The changes of urine flow are concordant with those of glomerular filtration, but are of a higher order. The divisions of the ordinate are therefore 10 times smaller in value than those of the abscissa.

four experiments which we have presented in detail, the flow of urine and the clearance of inulin ran roughly parallel in all our patients. In normal subjects glomerular filtration gradually fell with the nocturnal decline of diuresis, and rose in the subject who had nocturia. Among the three normal subjects of sub-group 3 there was a slight gradual increase of glomerular filtration. Changes of the same character, but more pronounced, were present in the compensated, and even more in the decompensated, cardiac patients. In these patients, as opposed to normal subjects, they were parallel to the changes in renal blood-flow and preceded the corresponding changes in the output of urine.

Correlation between diuresis and glomerular filtration (Fig. 14). It is obvious from the data just presented that there is a time coincidence between the changes of urine flow and of glomerular filtration. Fig. 13 affords no information about the degree of this correlation; but a glance at Fig. 14, which summarizes our data as to the relationship between the percentage changes of urine flow and those of glomerular filtration, will show that the latter are of a lower order than

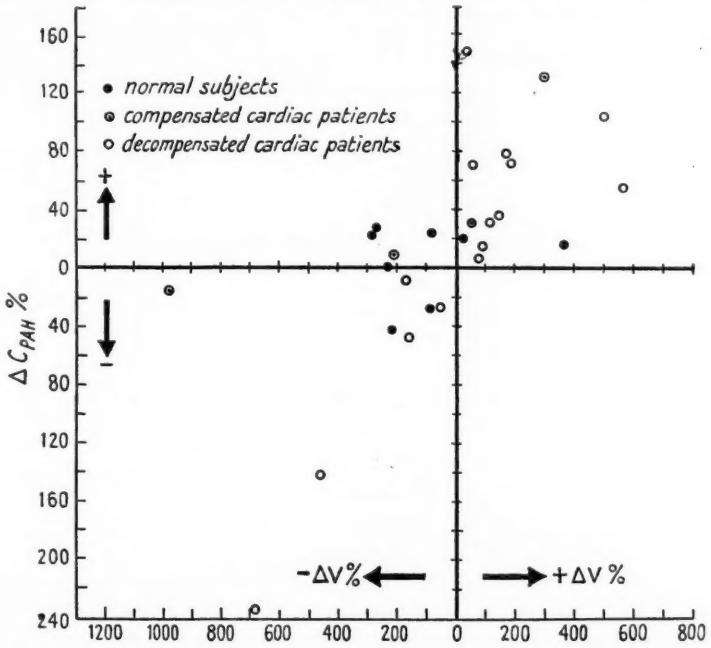

FIG. 15. Changes of urine flow (Δ V %) in relation to changes of renal plasma-flow (Δ C_{PAH} %) in normal and in cardiac subjects. The construction of the diagram is analogous to that of Fig. 14.

the former. Consequently the changes in glomerular filtration are inadequate to explain the total change in urine flow. Variations in the tubular reabsorption of water are therefore the more important of the two renal mechanisms participating in the formation of urine. This has already been shown in our description of individual experiments.

Correlation between diuresis and renal plasma-flow (Fig. 15). We have already shown that, while there was no definite relationship between renal blood-flow and flow of urine in normal subjects, such a relationship existed in patients with heart disease. It was important to discover whether the changes in renal plasma-flow and in urine flow were of a corresponding order. That this was not so is evident from the data in Fig. 15. The percentage changes of urine flow are of a much higher order than those of renal plasma-flow. In the decompensated, and in the majority of compensated, cardiac patients all the points are situated in the right upper and left lower quadrants, confirming the fact

that the fluctuations of renal plasma-flow and of urine flow ran parallel. In four normal subjects and in one fully compensated cardiac patient the points are situated in the left upper quadrant, showing that the two functions were not correlated.

Filtration fraction (Fig. 16). Fig. 16 summarizes our data as regards the

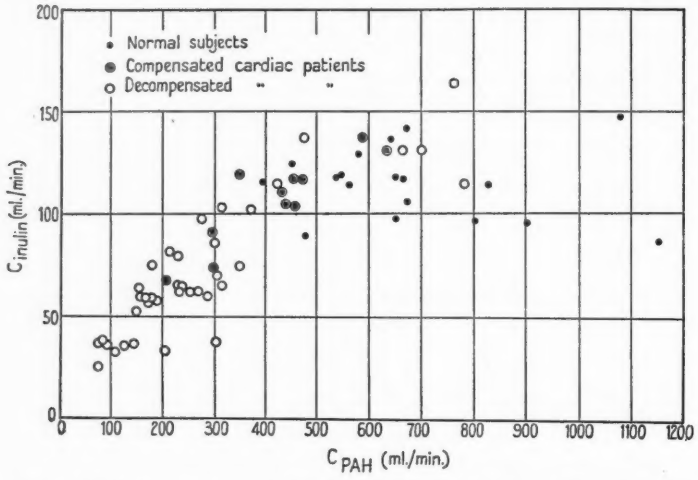

FIG. 16. Relationship between the rate of glomerular filtration (clearance of inulin) and renal plasma-flow (clearance of *p*-aminohippuric acid) in normal and in cardiac subjects. The filtration fraction $\left(\frac{C_{inulin}}{C_{PAH}}\right)$ obviously decreases with increasing renal plasma-flow.

relationship of the rate of glomerular filtration to renal plasma-flow, i.e. the filtration fraction, in all our subjects. These data confirm the findings of previous authors (Merrill, 1946; Mokotoff, Ross, and Leiter, 1948) that the filtration fraction in patients with heart disease is high. It is closely related to the rate of renal plasma-flow; whenever the latter increases the filtration fraction approaches a normal value. We demonstrated that a spontaneous increase of urine flow in cardiac patients was always associated with an increase of renal plasma-flow, the latter being accompanied in every case, without exception, by a fall of the filtration fraction (Fig. 17). In normal controls, and in some fully compensated cardiac patients, the opposite was true: the filtration fraction was normally lower with a low than with a high urine flow.

Discussion

Our basic assumption that, in cardiac patients, oliguria is an expression of the retention of fluid in the body and diuresis reflects a tendency to establish a normal water balance, seems to be backed up by old clinical experience. It is well known that a spontaneous diminution of urine heralds the appearance of oedema, and that its spontaneous increase is one of the first signs of clinical

improvement. A spontaneous change of urine flow in these patients may therefore be taken to reflect a changing water balance in the body. All our 35 patients were treated in the same way. Yet only 10 cardiac patients in failure showed a nocturnal diuresis associated with changes which differed markedly from those observed in the other patients, whose urine flow either did not change

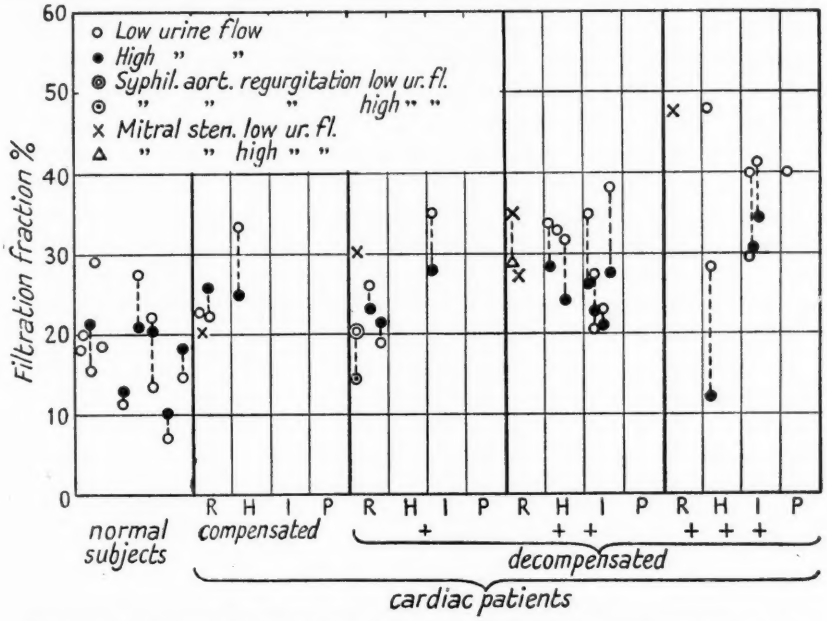

FIG. 17. Filtration fraction in normal and in cardiac subjects; the latter are divided into four groups according to their state of compensation assessed on clinical grounds. Each group is further subdivided into rheumatic (R), hypertensive (H), ischaemic (I), and pulmonary (P). Patients with a predominant mitral stenosis, and one with aortic regurgitation of syphilitic origin, have a distinctive mark; in the remaining patients of the rheumatic group aortic regurgitation was predominant. The dotted lines connect individual subjects at high and low urine flows.

or declined at night. These changes also stood in sharp contrast to those found in one normal subject and in one fully compensated cardiac patient, in whom diuresis occurred in the day, shortly after their afternoon meal, and was preceded by a marked haemodilution. The time of its appearance and the changes in the blood-plasma make it likely that the increased urine flow in these two subjects was due to fluid taken at the afternoon meal, and was a water diuresis. A similar behaviour of the blood-plasma, and an analogous time relationship, suggest that the same was true of three decompensated cardiac patients, whose low urine output showed a brief rise in the early hours of the evening. The quite different nocturnal diuresis of 10 cardiac patients could not be attributed to a higher fluid intake, and was not preceded by any haemodilution. It is therefore to be regarded as spontaneous, and as indicating a mobilization of fluid stored in the body.

The greatest care was taken to avoid errors in technique. Objections might be raised in particular to the validity of the PAH clearance as a measure of renal plasma-flow in cardiac subjects, to the methods used to assess the water-content of the plasma, and to the right auricular pressure as a reflection of the pressure at the venous end of the capillaries. That the renal extraction of *p*-aminohippurate is complete even in cardiac disease with failure was demonstrated by Warren, Brannon, and Merrill (1944). The validity of the PAH clearance test has thus been confirmed. The changes in the water-content of the plasma were measured simultaneously by three independent methods; the variations were often at the limit of technical error, and therefore only changes in the same direction registered by at least two of the three methods were considered significant. It is possible, and even likely, that venous tone is different in various parts of the venous system. But the first consequence of an impeded ability of the heart to promote the flow of blood from the venous system, as postulated by Starling's theory, must be a rise of pressure in the right auricle. The reliability of the other methods employed has been discussed in numerous papers to which space forbids detailed reference.

These technical considerations settled, we can go on to discuss our experimental results. The data presented allow the following conclusions to be drawn.

1. No consistent changes in right auricular pressure precede the spontaneous changes of urine flow or of renal blood-flow in cardiac patients with failure. After such changes of urine flow, the changes which we observed in right auricular pressure were more consistent, the pressure tending to rise as the output of urine declined and vice versa. Changes in the right auricular pressure cannot therefore be considered the primary cause of the spontaneous changes which occur in the urine flow and renal blood-flow of cardiac patients.

2. A slight haemodilution occurs at night both in normal subjects and in patients with heart disease, when their output of urine is either unchanged or diminished by night as compared with day. This haemodilution does not bring about any increase in urine flow.

3. A marked haemodilution was observed in one normal subject and in four cardiac patients late in the afternoon or early in the evening, with an increase in urine flow. The water-content of their plasma later fell to the level it would have had if no such diuresis and haemodilution had occurred. After the diuresis declined there was a gradual increase in the water-content of the plasma, indistinguishable from the haemodilution mentioned under (2).

4. Cardiac patients with failure whose urine flow increased spontaneously at night showed the same degree of haemodilution before diuresis, during the oliguric period, as the subjects mentioned under (2) whose urine flow was low. This haemodilution cannot, therefore, be considered the factor responsible for their spontaneous diuresis. This diuresis, on the contrary, was probably produced, at least in its initial stage, at the expense of the plasma-water. This seems evident from the subsequent haemoconcentration. A secondary inflow of extracellular fluid into the blood later replaced this lost fluid, as was shown by the return of the water-content of the plasma to its original value.

5. No fixed relationship exists between the renal blood-flow and the urine flow in normal subjects. In patients with heart failure the renal blood-flow is low; its increase invariably precedes the onset of diuresis, and its decline precedes a diminished flow of urine.

6. No constant relationship exists between the changes in cardiac output and those of renal blood-flow. The observation of previous authors (Merrill, 1946; Mokotoff, Ross, and Leiter, 1948), that the renal fraction is very low in patients with heart failure, has been confirmed. The renal fraction in these patients invariably increases when the urine flow increases, and falls with a diminution of urine, although in the majority of heart patients even its highest values remain below the normal range. It follows that the changes of renal blood-flow in cardiac patients are not brought about by corresponding changes of cardiac output. They are the result of a changed distribution of blood. The blood-supply to the kidneys is very low during the oliguric phase, and improves just before diuresis.

7. The changes in glomerular filtration run parallel with the changes in urine flow both in normal and in cardiac subjects. They account, however, only for a small fraction of the total diuretic change. Its greater part is therefore due to simultaneous changes in water reabsorption, which falls when filtration increases and vice versa.

8. The conclusion of other authors (Merrill, 1946; Mokotoff, Ross, and Leiter, 1948), that the filtration fraction is high in cardiac patients with failure, was confirmed. Whenever spontaneous diuresis occurred the filtration fraction fell. Its behaviour in normal subjects was not consistent, but was usually opposite to that found in cardiac patients.

Returning to our schematic representation of the sequence of events in cardiac patients with failure when retained water is released from the body, we can see that our results do not fit into Starling's back pressure theory. Although a superficial glance at the experiment presented in Fig. 5 might suggest that the elimination of fluid follows a previous influx of extracellular fluid into the blood, a general survey of all our experiments clearly demonstrates that this is not true. In most normal and cardiac subjects, as Perera and Berliner showed (1943) and our own data suggest, there is a haemodilution at night. But spontaneous nocturnal diuresis occurred only in some of our cardiac patients, and up to the moment of its onset the changes recorded in the water-content of their plasma were indistinguishable from those observed in other subjects, in whom the output of urine at night was unchanged or even diminished. The subsequent haemoconcentration occurring in patients with nocturia suggested that the diuresis was a primary factor, and the influx of extracellular fluid into the blood a secondary event following upon the renal loss of fluid. The increased renal blood-supply which invariably preceded this increased output of water must be considered a factor of primary importance in the diuresis of cardiac patients. As we have already seen, it is not the result of an increased cardiac output, but is effected by a redistribution of blood, which during the oliguric period is diverted from the kidneys to other tissues. This diversion is the primary event in the

disturbed water balance of cardiac patients, and leads to a retention of fluid in the body. The return of the diverted blood to the kidneys starts the reverse process.

The reason for this diversion of blood from the kidneys is obviously not to be

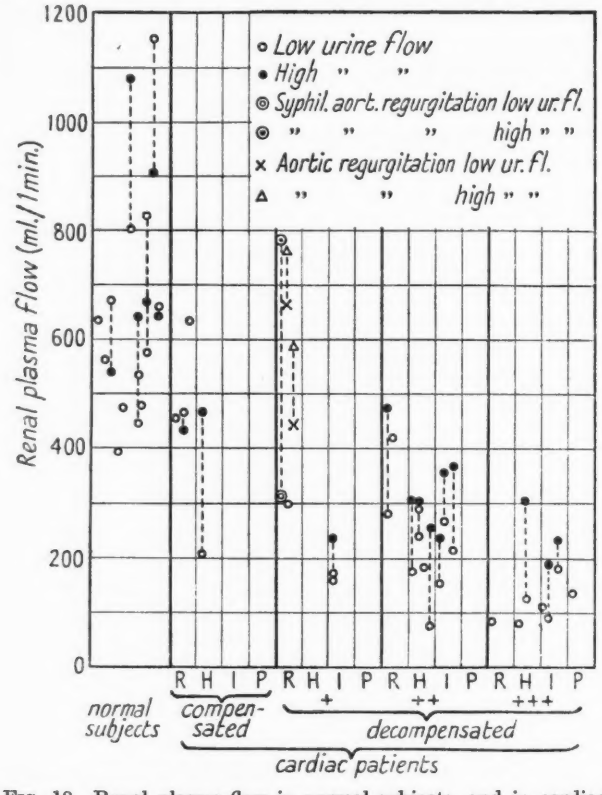

FIG. 18. Renal plasma-flow in normal subjects, and in cardiac patients with different degrees of compensation. The groups are the same as in Fig. 17.

found in changes of venous pressure, nor have we found it directly related to the level of cardiac output. A low renal fraction was observed in some of our cardiac patients in spite of a very high cardiac output; in one patient with cor pulmonale and severe right-sided heart failure the cardiac output amounted to 11,200 ml. per minute, while the highest renal blood-flow recorded was 463 ml. per minute, giving a renal fraction of 4·13 per cent. This speaks strongly against Borst's suggestion (1948) that a low sodium and chloride output is a compensatory measure by which the kidneys try to raise a falling cardiac output. We gained the impression, however, that the reduction of renal blood-flow was related to the degree of circulatory failure. Some such reduction was present in cardiac patients who had no major clinical signs of failure. Although the degree of heart failure in our subjects was assessed on purely clinical grounds

(the duration of illness, the severity of dyspnoea and of oedema, the frequency of paroxysmal nocturnal dyspnoea, and the response to treatment), and before we had any knowledge of our experimental data, the PAH clearance values showed a continuous descent with the progressive impairment of heart function (Fig. 18).

Merrill (1946) suggested that the reduction of renal blood-flow in cardiac disease is due to an efferent arteriolar spasm. This suggestion was based on the finding of a high filtration fraction, which was ascribed to high pressure in the glomerular capillaries. We found that the filtration fraction invariably decreased with an increase of renal blood-flow. This decrease would point to a relaxation of the efferent arteriolar tone, which in its turn would allow more blood to flow through the kidney. So far we do not know the cause of this efferent arteriolar spasm. The only experimental evidence on this point originates from Mokotoff and Ross (1948), who concluded that the mechanism was not neurogenic. Two other possible explanations of the renal haemodynamic changes suggest themselves. The first is that the extraction of *p*-aminohippuric acid from the blood in cardiac patients with failure is incomplete, so that the estimate of renal plasma-flow from PAH clearance is too low. An increase in PAH clearance at night and a fall in the filtration fraction would then simply mean that the extraction has improved. But, as we have already pointed out, Warren, Brannon, and Merrill (1944) found the extraction of *p*-aminohippuric acid in cardiac failure to be almost complete. It is also difficult to imagine by what mechanism a low extraction should increase at night, save by an improved blood-supply to the kidney. As a second possibility we have to consider para-glomerular shunts, the existence of which has been proved by Fuchs and Popper (1937, 1938), Spanner (1937), and in a certain sense also by Trueta, Barclay, Daniel, Franklin, and Prichard (1947). An increased blood-supply flowing through these channels could be cleared of *p*-aminohippuric acid by tubular secretion, and so contribute to PAH clearance. At the same time the glomerular circulation might be increased only to a small extent, proportionate to the increase of inulin clearance. The true filtration fraction would then remain unaffected, being as high during diuresis as during the oliguric period; but owing to the tubular increment of PAH clearance we should get a virtual fall of the filtration fraction. According to Fuchs and Popper (1938), blood which has by-passed the glomeruli opposes by its filtering tendency the reabsorptive force of the post-glomerular blood, which has already lost fluid in the glomerular capillaries. It may easily be calculated that (should this view be correct) a very small increment of para-glomerular plasma-flow would markedly reduce tubular reabsorption. The increments of renal blood-flow observed in our experiments, if para-glomerular, would produce a much greater decrease in the inulin U/P ratio than was actually found. Our experimental data thus favour the conclusion that the greater part of the increment of renal blood-flow is glomerular, and that the fall in the filtration fraction reflects a decrease of efferent arteriolar tone. The remaining possibility, that the high filtration fraction in cardiac patients is due to increased venous pressure, has already been rejected.

The possibility that the oliguria and low glomerular filtration of cardiac disease is due to a by-pass of renal blood through Trueta's juxta-medullary glomeruli (Trueta, Barclay, Daniel, Franklin, and Prichard, 1947), and that an increase of the inulin and PAH clearance means a return of blood to the cortical glomeruli, is not compatible with our results. Since the pressure is much higher in the cortical than in the juxta-medullary glomeruli, nocturnal diuresis should be associated with an increase rather than with a fall in the filtration fraction. The question remains whether the decrease in the tubular reabsorption of water, which always contributes to spontaneous diuresis in cardiac patients, is of post-pituitary origin, and due to an inhibition of the secretion of antidiuretic hormone. This inhibition might reflect a change in the water balance of the body, which would thus try to rid itself of surplus water. However, the time coincidence of the increase in renal plasma-flow and the fall in tubular reabsorption of water is striking, and we have already shown that a very small increment of para-glomerular blood-flow would account sufficiently for a marked inhibition of the tubular reabsorption of water.

Of the two mechanisms taking part in the production of urine, it follows from our data that the more important in causing spontaneous diuresis in cardiac patients is inhibition of the tubular reabsorption of water. This applies especially to subjects with sclerotic renal vessels, in whom the increase of glomerular filtration is often almost negligible.

We can briefly summarize our experimental evidence as follows: if we are right in assuming that the oliguria in cardiac patients is an expression of the retention of water in the body, and that spontaneous diuresis in these patients reflects a tendency to re-establish a normal water balance, we must conclude that the primary event in the production of this disturbance of water balance is an impairment of renal blood-flow due to efferent arteriolar spasm. This takes place irrespective of changes in venous pressure which, if they occur, are of a secondary nature. The immediate consequence of this reduction of renal blood-flow is a fall in the output of urine, and a retention of electrolytes and water in the body. The reduction of renal blood-flow is not due to a concomitant diminution of the cardiac output. It is obviously related, however, to the degree of heart failure, and is brought about by a new distribution of the available blood, which is shifted from the kidneys to those organs and tissues whose oxygen-need during increased activity cannot be satisfied by the failing heart. This emergency distribution of blood is no longer needed during complete rest at night, when the great call for oxygen from the muscles and other organs has stopped. Consequently, blood can return to those organs and tissues whence it has been drained during the state of emergency. This results in an increased renal blood-flow and an improvement in the renal excretion of electrolytes and water, which have been retained in the body during the day. Nocturia can thus be regarded as a compensatory measure. The emergency distribution of blood is a very early event, and nocturia is one of the first symptoms of a failing heart. When the degree of heart failure is such that a considerable oxygen debt is maintained even during complete rest at night, the emergency distribution of

blood remains fixed throughout the 24 hours (Fig. 6). The nocturnal tide of blood to the kidneys does not take place, nocturia is absent, and accumulation of fluid in the body becomes a prominent feature of the disease.

We wish to express our gratitude to Miss M. Bartošová, Senior Sister in the First Medical Clinic, and Mr. V. Rábek who assisted us in the preparation of the experiments and in the laboratory work. The investigation was made with the help of grants from Czechoslovak United Pharmaceutical Industries and the Ella Sachs Plotz Foundation, Boston, U.S.A.

Summary and Conclusions

1. The changes in cardiac output, right auricular pressure, water-content of the plasma, and renal function which occurred during a spontaneous change in urine flow from low to high or vice versa, were studied in 10 normal subjects and in 25 patients with heart disease.

2. Reasons have been given for the belief that such a spontaneous change, at least in cardiac patients, reflects a changing water balance in the body.

3. Spontaneous changes in urine flow were not preceded by any consistent change in the right auricular pressure either in normal or in cardiac subjects. Changes in the right auricular pressure cannot therefore be considered to be the cause of the disturbed water balance in cardiac patients.

4. In decompensated cardiac patients oliguria is due to a diminished renal blood-flow, and spontaneous diuresis is always preceded by an increase of renal blood-flow.

5. This spontaneous diuresis is brought about by an increase in the originally low glomerular filtration and by an inhibition of the tubular reabsorption of water. Both these mechanisms depend strictly on changes in the renal blood-flow. The changes in tubular reabsorption are the greater factor in the production of diuresis.

6. The low renal blood-flow is due to an efferent arteriolar spasm, which is shown by a high filtration fraction. The spontaneous diuresis of cardiac patients is always accompanied by a fall, and its decline by a rise, of the filtration fraction.

7. Changes of the renal blood-flow in cardiac patients are not due to concomitant changes in the cardiac output. The reduction of renal blood-flow in decompensated heart disease is due to an emergency distribution of the available blood, which is drained away from the kidneys during periods of increased activity. Spontaneous nocturnal diuresis occurs in some cardiac patients with a slight or moderate degree of failure, and is brought about by a return of blood to the kidneys during the period of complete rest.

8. Moderate haemodilution always occurs when the urine flow is low. It is not followed by diuresis. The haemodilution which precedes spontaneous diuresis in cardiac patients is of the same degree, and cannot therefore be the cause of this diuresis.

9. A marked transient haemoconcentration occurs in cardiac patients shortly after diuresis begins, suggesting that the initial increase of urine flow takes place at the expense of water in the plasma.

10. In patients with severe heart failure and decreased cardiac output, the emergency distribution of blood persists day and night.

11. In these patients a reduced renal blood-flow is a permanent feature, leading to the accumulation of salt and water in the body.

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612.461.61:616.12-008.46

THE EXCRETION OF CHLORIDES IN PATIENTS WITH HEART FAILURE[1]

By ZDENĚK FEJFAR and JAN BROD

With the technical assistance of Evženie Kotanová

(From the Department of Medicine, State Hospital, Motol-Praha, and the First Medical Clinic, Charles University, Praha, Czechoslovakia)

Introduction

It has long been known from clinical experience that there is a connexion between the intake of salt and the formation of oedema in patients with heart disease. Widal (1909) recognized the beneficial effect of a salt-free diet on the oedema of congestive heart failure. But the basis of this therapeutic procedure was unknown, and it was not much stressed in clinical practice. Much greater importance was attached to the restriction of fluids. This was largely because, according to the prevalent back-pressure theory, salt had no place in the mechanism of oedema formation. Recent work has cast some doubt on the correctness of this theory. Warren and Stead (1944) concluded from their observations that the inability of the kidneys to excrete salt must be the primary cause of oedema. A diminished renal blood-supply in heart disease was found by Merrill (1946), and was thought to account for this disturbance of excretion. Mokotoff, Ross, and Leiter (1948) studied the excretion of sodium in patients with congestive heart failure, and confirmed the fact that such an inability really existed; they found that the tubules reabsorbed a constant high proportion of the filtered sodium, irrespective of the amount of glomerular filtration. With a diminished glomerular filtration this resulted in retention of sodium in the body.

All the evidence presented so far has been based on static experiments and observations, which describe an established equilibrium without any reference to its genesis. A diminished output of sodium and chloride might be due to an inability of the kidneys to excrete extracellular electrolytes; but the same effect could be produced by a disturbed water balance in the tissues, in the so-called *Vorniere* of Volhard (1931). The question can only be decided by experimental observations which register the development or spontaneous recession of the disturbance of water balance in cardiac disease. We have therefore tried to follow the sequence of events in patients with congestive heart failure at the moment when the water balance is changing. For this purpose we have recorded the processes associated with the spontaneous diuresis which occurs with great regularity in many cardiac patients at night. If oliguria is the expression of water-retention in the body, this spontaneous

[1] Received September 28, 1949.

TABLE I

Renal Elimination of Chlorides in Subjects with Normal Heart and Kidneys

Case number	*Patient*	*Sex*	*Age (years)*	*Body-surface area (sq. m.)*	*Diagnosis*	*Urine flow (V) (ml./min.)*	*Glomerular filtration ($C_{inul.}$) (ml./min.)*	*Chlorides*										
								in plasma (P_{Cl}) (mEq/1,000 ml.)	*filtered ($P_{Cl} \times C_{inul.}$) (mEq/min.)*	*in urine (U_{Cl}) (mEq/1,000 ml.)*	*excreted ($U_{Cl} \times V$) (mEq/min.)*	*reabsorbed (T_{Cl}) (mEq/min.)*	*reabsorbed per 100 ml. of glomerular filtrate (mEq)*	*reabsorbed per 100 mEq filtered chloride $\left(\frac{T_{Cl}}{P_{Cl} \times C_{inul.}} \times 100\right)$*	*Chloride clearance (C_{Cl}) (ml./min.)*	$\frac{C_{Cl}}{C_{inul.}} \times 100$	*Water reabsorbed per 100 ml. glomerular filtrate $\left(\frac{T_{H_2O}}{C_{inul.}} \times 100\right)$*	*Chloride/water reabsorption ratio $\left(\frac{col.\ o}{col.\ r}\right)$*
a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*	*j*	*k*	*l*	*m*	*n*	*o*	*p*	*q*	*r*	*s*
1	Bor.	F	28	1·55	Functional dyspepsia	0·51	117·0	104·7	12·23	88·65	0·050	12·18	10·39	99·4	0·478	0·408	99·5	99·8
2	Bog.	F	28	1·46	Hodgkin's disease	0·36	115·2	111·7	12·85	99·7	0·0425	12·808	11·1	99·5	0·381	0·331	99·4	100·1
3	Kad.	F	18	1·54	Normal	0·78	119·5	116·2	13·90	84·0	0·0737	13·826	11·56	99·4	0·633	0·53	99·2	100·2
						0·43	107·0	116·2	12·43	60·78	0·0293	12·401	11·58	99·7	0·252	0·235	99·6	100·1
4	Fra.	M	40	1·76	Post-pneumonic	1·38	115·8	110·6	12·8	202·9	0·2755	12·524	10·80	97·8	2·49	2·15	98·8	98·9
5	Fru.	F	19	1·53	Normal	0·438	90·0	108·8	9·79	172·0	0·0852	9·705	10·77	99·1	0·784	0·871	99·5	99·7
6	Kau.	M	37	1·78	Normal	1·02	148·2	105·1	15·60	163·4	0·162	15·438	10·42	99·0	1·54	1·04	99·3	99·7
						0·55	97·6	105·4	10·3	107·8	0·0577	10·242	10·49	99·6	0·547	0·561	99·5	100·1
7	Ště.	F	19	1·59	Normal	0·561	119·5	107·8	12·89	136·7	0·0836	12·806	10·71	99·4	0·776	0·649	99·3	100·2
						2·017	137·0	107·6	14·7	38·35	0·0839	14·616	10·68	99·5	0·78	0·568	98·5	101·0
						0·643	125·0	109·0	13·6	63·6	0·0446	13·555	10·82	99·5	0·408	0·327	99·5	101·0
8	Vac.	F	18	1·45	Normal	0·607	130·0	102·8	13·8	187·5	0·1358	13·6642	10·51	98·9	1·32	1·014	99·4	99·5
						2·83	135·3	103·0	13·9	57·5	0·1941	13·706	10·13	98·7	1·882	1·392	97·8	100·9
						0·618	115·5	100·0	11·55	158·9	0·1171	11·433	9·90	98·9	1·117	1·013	99·4	99·6
9	Kov.	M	29	1·87	Normal	2·026	96·2	101·07	9·73	154·3	0·289	9·441	9·83	97·0	2·86	2·97	97·9	99·1
						0·583	88·0	99·0	8·72	66·8	0·03588	8·684	9·87	99·6	0·350	0·398	99·3	100·2
10	Šná.	F	19	1·73	Normal	2·38	119·5	103·9	12·4	78·3	0·1865	12·213	10·21	98·5	1·795	1·503	98·0	101·3
						0·682	99·2	102·4	10·18	150·1	0·1025	10·077	10·10	99·0	1·002	1·010	99·3	99·7
													Mean 10·54					

All the figures are averages of several observation periods either of low or of high output of urine, and are reduced to a body surface of 1·73 sq. m. The total amount of water reabsorbed from the tubules (T_{H_2O}) is the difference between the amount of glomerular filtrate (col. *h*) and the quantity of urine per minute (col. *g*).

onset of diuresis should mean that the factors responsible for water-retention are receding, and a change to oliguria that they are increasing. In a series of experiments recorded in the preceding article (Brod and Fejfar, 1950) we produced evidence that a shift of blood from the kidneys during the day is of primary importance in the formation of oedema in cardiac patients, and that nocturia is brought about by a nocturnal tide of blood to the kidneys. In our preliminary observations we were struck by the fact that the nocturnal diuresis of cardiac patients, in contrast to water diuresis, is associated with a high chloride excretion. The urinary concentration of chlorides increases with the increased flow of urine. The present paper deals with the mechanism of the renal elimination of chlorides in cardiac patients when the urine flow is diminished, and when it is spontaneously increased at night.

Methods

Our experiments were carried out in 10 normal subjects and in 25 patients with heart disease. A detailed description of our experimental material and technique is given in the preceding paper. Samples of urine and blood were collected at intervals varying from 10 to 60 minutes. Glomerular filtration was measured by the inulin clearance, and the rate of tubular reabsorption of water by the inulin concentration index (U/P ratio). Plasma- and urine-chlorides were estimated by the Van Slyke and Hiller (1947) modification of Sendroy's iodometric method. Chloride clearances were calculated for each period of urine collection; the representative plasma-chloride values were found by interpolation between adjacent estimations, allowing two and a half minutes for the passage from the glomeruli to the bladder. The plasma-chloride levels varied very little throughout the experiment. In evaluating our data it was found advantageous to average the results obtained (1) at periods of low and (2) at periods of high urine flow. The quantity of chloride filtered was calculated as the product of the rate of glomerular filtration ($C_{\text{inul.}}$) and the concentration of chlorides in the glomerular filtrate, which is equal to that in the plasma ($P_{\text{Cl}'}$). The small factor for Donnan's equilibrium (Wesson and Anslow, 1948) was neglected. Similarly the quantity of chloride excreted per minute was calculated as the product of urinary chloride concentration ($U_{\text{Cl}'}$) and the rate of urine flow (V, ml. per minute). The difference between chloride filtered and chloride excreted gives the amount of chloride reabsorbed per minute ($T_{\text{Cl}'}$). The concentration of chlorides in the reabsorbed fluid can be found by dividing $T_{\text{Cl}'}$ by the quantity of fluid which is reabsorbed per minute, i.e. by the difference between the amount of fluid filtered and excreted.

Results

Table I summarizes our data regarding the renal excretion of chlorides in 10 normal individuals. In six of them we were able to make our observations during periods both of low and of high urine flow. In every case glomerular filtration was higher at high than at low urine flows, although the changes in

volume of urine much exceeded those of glomerular filtration. Plasma-chloride levels in any given individual differed very little between the periods of low and those of high urine output. Consequently the quantity of chlorides filtered varied in direct proportion to the inulin clearance. The amount of chloride excreted varied between 0·03 and 0·28 milliequivalents per minute. As a rule it was lower when urinary output was low and higher when it increased. An exception was found in one patient (Case 7), in whom a quadrupling of urine output and a significant change in glomerular filtration were not accompanied by any fluctuation in the amount of chloride excreted. But a later fall of the urine flow almost to its original level was associated with a decrease of the excreted chloride to about half of its previous value. In the remaining patients the question might arise whether the amount of chloride excreted was proportionate to the amount filtered by the glomeruli, and consequently to the inulin clearance. A glance at the chloride/inulin clearance ratio (column *q*) shows that this was not so. At high urine flows the chloride clearance increased out of proportion to the rate of glomerular filtration. The ratio of the chloride to the inulin clearance, which was below 1 per cent. at urine volumes of less than one ml. per minute in nine cases out of 12, increased with a single exception to above 1 per cent. whenever the urine flow exceeded one ml. per minute. In Case 7 the ratio fell slightly when diuresis increased, suggesting that more chloride was reabsorbed. These facts are also evident from column *o*, which shows the percentage of the filtered chloride which was reabsorbed. Its value increased slightly as the urine flow decreased in Cases 3, 6, 8, 9, and 10, while in Case 7 there was a slight increase in chloride reabsorption with increasing urine flow. In this subject the diuretic change occurred about one hour after a considerable intake of fluid (about 550 ml.) and was probably due to it. This seems to be borne out by the fact that a marked haemodilution preceded the onset of her diuresis (the plasma-proteins fell from 6·64 to 6·11 per cent.).

It can be seen that even at a very high urine flow the great bulk of the filtered chloride is reabsorbed. Most of the chloride reabsorption values which we observed were above 99 per cent. Reabsorption did not fall below 97 per cent. of the amount filtered even in the patient (Case 9) who excreted the greatest quantity of chloride. But because the quantity normally escaping reabsorption is so very minute, this small percentage change can produce great changes in the chloride output. At an almost constant plasma-chloride level these changes will be accompanied by equally marked changes in the chloride clearance. On the other hand, the range of variations in chloride reabsorption is so small that when it is plotted against glomerular filtration a practically linear relationship, similar to that found by Mokotoff, Ross, and Leiter (1948), results. This creates the impression that a constant fraction of 10·54 milliequivalents of chloride is reabsorbed from every 100 ml. of the glomerular filtrate (Fig. 1). The approximate ratio of chloride to sodium in the extracellular fluid is 110 milliequivalents of chloride to 140 of sodium. If this proportion is preserved in the tubular urine and in the reabsorbed fluid, the quantity of sodium corresponding to 10·54 mEq Cl′ is 13·42 mEq Na. This is in good agreement with the

value 13·3 mEq Na found by Mokotoff, Ross, and Leiter (1948) for the reabsorbed sodium per 100 ml. of glomerular filtrate.

The data obtained in 25 cardiac patients are presented in Table II. There was no evidence of heart failure in Cases 22, 24, 27, or 33, and in Cases 25 and 28 the signs of heart failure were very slight. In these patients, in Case 34 (aortic regurgitation), and in Cases 19 and 20 (rheumatic heart disease and mitral

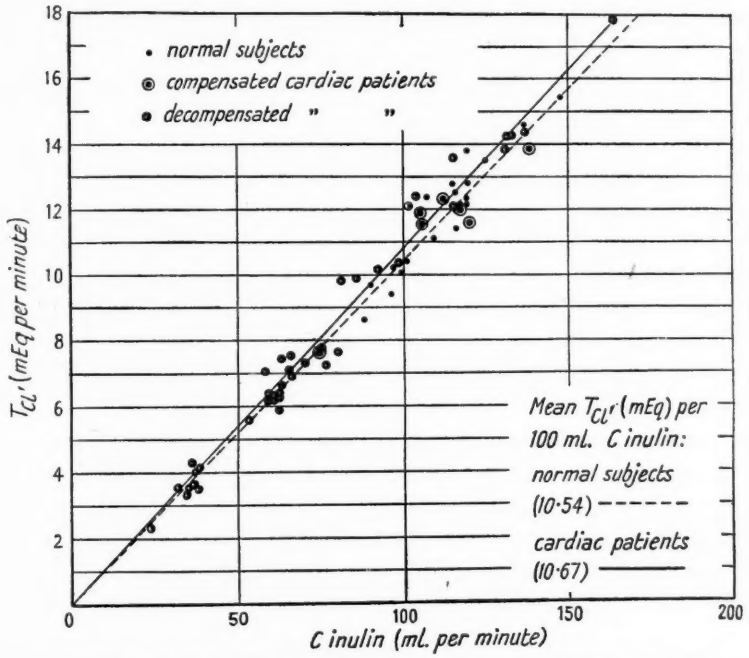

FIG. 1. The rate of glomerular filtration (clearance of inulin) related to the amount of chloride in milliequivalents reabsorbed per minute ($T_{Cl'}$). There is no significant difference between normal and cardiac patients in the amount of chloride reabsorbed per 100 ml. of glomerular filtrate.

stenosis) glomerular filtration was normal. These last three patients had no clinical signs of oedema at the time of observation. In the remaining patients glomerular filtration was subnormal and symptoms and signs of heart failure were present. This low glomerular filtration increased at night whenever there was a spontaneous increase in urine flow. The plasma-chlorides were within normal limits. Consequently the quantity of filtered chloride in patients with a low glomerular filtration was far below that in normal subjects. A normal rate of chloride filtration was approached in some of them (Cases 11, 12, and 21), when glomerular filtration increased at night. A glance at column *o* will show once more that a very high proportion of the filtered chlorides was reabsorbed. The average figure for the whole group of 10·67 mEq total chloride reabsorption per 100 ml. of glomerular filtrate does not differ significantly from that found

TABLE II

Renal Elimination of Chlorides in Subjects with Heart Disease

Case number	*Patient*	*Sex*	*Age (years)*	*Body-surface area (sq. m.)*	*Diagnosis*	*Urine flow (V) (ml./min.)*	*Glomerular filtration ($C_{inul.}$) (ml./min.)*	*Chlorides*									
								in plasma (P_{Cl}) (mEq/ 000 ml.)	*filtered ($P_{Cl} \times C_{inul.}$) (mEq/min.)*	*in urine (U_{Cl}) (mEq/1,000 ml.)*	*excreted ($U_{Cl} \times V$) (mEq/min.)*	*reabsorbed (T_{Cl}) (mEq/min.)*	*reabsorbed per 100 ml. of glomerular filtrate (mEq)*	*reabsorbed per 100 mEq filtered chloride $\left(\frac{T_{Cl}}{P_{Cl} \times C_{inul.}} \times 100\right)$*	*Chloride clearance (C_{Cl}) (ml./min.)*	$\frac{C_{Cl}}{C_{inul.}} \times 100$	*Water reabsorbed per 100 ml. glomerular filtrate $\left(\frac{T_{H_2O}}{C_{inul.}} \times 100\right)$*	*Chloride/water reabsorption ratio $\left(\frac{col.\ o}{col.\ r}\right)$*
a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*	*j*	*k*	*l*	*m*	*n*	*o*	*p*	*q*	*r*	*s*
11	Voj.	F	45	1·60	SHD, AR, LF	0·87	65·3	116·5	7·60	82·25	0·078	7·522	11·5	99·0	0·671	1·028	98·6	100·3
						1·33	115·3	118·7	13·7	88·0	0·127	13·573	11·75	98·9	1·070	0·928	98·8	100·0
12	Hav.	F	59	1·60	HHD, emphysema, cor pulmonale, RF	0·76	58·1	124·0	7·20	200·1	0·165	7·035	12·1	97·7	1·33	2·285	98·6	99·1
						2·04	86·5	120·5	10·42	232·5	0·514	9·906	11·44	95·0	4·26	4·93	97·8	97·1
13	Scho.	F	68	1·70	IHD, LF, RF	0·472	53·0	107·0	5·67	216	0·1038	5·566	10·52	98·2	0·971	1·83	99·1	99·1
						3·13	62·0	105·0	6·51	182·9	0·583	5·927	9·57	91·2	5·55	8·95	95·0	95·9
14	Rez.	F	68	1·17	IHD, RF	0·67	32·4	112·5	3·65	99·5	0·0986	3·551	10·95	97·2	0·876	2·70	97·8	99·3
15	Hup.	F	68	1·52	Bronchiectasis, cor pulmonale	0·65	60·1	105·0	6·32	50·68	0·0420	6·278	10·43	99·4	0·400	0·665	98·8	100·5
						1·18	70·3	105·4	7·42	84·6	0·1139	7·306	10·40	98·5	0·983	1·398	98·4	100·1
						0·76	65·4	109·0	7·13	80·1	0·0693	7·061	10·82	99·0	0·635	0·971	98·9	100·2
16	Fro.	F	61	1·67	IHD, LF, RF	0·51	59·6	107·8	6·42	58·6	0·031	6·389	10·72	99·4	0·288	0·483	99·1	100·2
						1·26	65·7	107·8	7·08	91·3	0·1192	6·961	10·60	98·3	1·105	1·68	97·9	100·3
						0·49	59·7	105·5	6·30	65·8	0·0334	6·267	10·48	99·6	0·316	0·529	99·1	100·4
17	Hov.	F	72	1·62	HHD, LF	0·81	59·5	107·5	6·4	99·7	0·0863	6·314	10·62	98·7	0·803	1·35	98·6	100·2
18	Nik.	F	70	1·54	IHD, LF	0·59	62·4	104·0	6·49	56·06	0·0372	6·453	10·35	99·5	0·358	0·574	99·0	100·5
						1·22	75·0	105·0	7·88	78·2	0·1073	7·773	10·35	98·7	1·023	1·37	98·3	100·5
19	Dyr.	F	47	1·73	RHD, MS, RF	0·53	98·0	102·5	10·05	163·9	0·0869	9·963	10·18	99·5	0·848	0·865	99·4	100·1
						0·83	137·5	106·0	14·51	181·8	0·1507	14·359	10·43	98·9	1·42	1·032	99·3	99·5
20	Zou.	F	43	1·71	RHD, MS, RF	0·84	115·0	105·8	12·18	106·35	0·0906	12·089	10·49	99·2	0·855	0·745	99·3	99·9
21	Kož.	F	64	1·52	IHD, RF	0·39	81·9	120·4	9·86	105·8	0·0468	9·813	12·00	99·4	0·3885	0·475	99·6	99·7
						0·77	103·7	120·4	12·50	116·07	0·1018	12·398	11·95	99·2	0·846	0·815	99·2	100·0
						1·11	102·2	120·4	12·32	146·2	0·185	12·135	11·85	98·4	1·535	1·50	99·0	99·4
22	Nov.	F	36	1·52	RHD, MR (compensated)	0·50	104·8	114·0	11·95	95·9	0·0567	11·893	11·35	99·4	0·497	0·474	99·6	99·7

a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*	*j*	*k*	*l*	*m*	*n*	*o*	*p*	*q*	*r*	*s*
23	Koc.	M	53	1·80	HHD, RF	0·39	37·5	108·7	4·07	61·9	0·0232	4·047	10·79	99·4	0·213	0·567	98·9	100·4
24	Něm.	F	19	1·53	RHD, MR (compensated)	1·83	112·5	111·3	12·55	80·1	0·1660	12·383	11·00	98·6	1·505	1·336	98·4	100·2
						0·59	105·5	111·8	11·80	171·1	0·1142	11·686	11·05	99·0	1·023	0·972	99·4	99·7
25	Hro.	F	33	1·39	RHD, MS, AR, RF±	0·90	92·0	110·7	10·18	58·6	0·0656	10·114	11·00	99·6	0·594	0·646	99·1	100·4
26	Kuč.	M	45	1·58	Fibrosis of lungs, RF	0·74	63·8	105·5	6·75	112·6	0·0914	6·659	10·44	98·5	0·865	1·355	99·0	99·5
27	Get.	F	27	1·56	RHD, MS (compensated)	1·96	131·2	106·1	13·92	29·8	0·0649	13·855	10·55	99·5	0·611	0·465	98·4	101·0
28	Sla.	M	52	1·78	RHD, AR, LF±	0·852	117·0	104·5	12·23	217·7	0·180	12·050	10·30	98·5	1·72	1·47	99·4	99·1
						1·29	138·2	102·0	14·1	213·8	0·268	13·832	10·00	98·2	2·623	1·892	98·9	99·3
29	Pol.	F	62	1·60	RHD, HHD, MS, LF	0·218	38·4	108·5	4·17	68·4	0·0161	4·154	10·82	99·7	0·1484	0·386	99·4	100·2
30	Pin.	F	57	1·45	IHD, LF, RF	1·62	58·0	118·75	6·89	63·3	0·122	6·768	11·67	98·4	1·280	2·21	97·2	101·1
						0·27	36·3	120·25	4·37	47·6	0·0153	4·355	11·99	99·7	0·127	0·35	99·2	100·4
31	Kob.	M	51	1·58	HHD, kyphoscoliosis, RF	2·61	38·1	99·3	3·78	77·5	0·221	3·559	9·34	94·1	2·195	5·75	93·2	101·0
						0·91	34·4	100·0	3·44	60·0	0·0597	3·420	9·94	99·4	0·597	1·737	97·4	102·0
						0·423	36·0	101·0	3·635	30·4	0·01405	3·621	10·06	99·7	0·1391	0·380	98·8	100·9
32	Pil.	F	64	1·53	IHD, LF, RF	0·379	75·0	96·0	7·20	37·1	0·0159	7·184	9·59	99·7	0·1654	0·221	99·5	100·1
						0·90	80·0	95·5	7·64	25·6	0·0261	7·614	9·52	99·6	0·273	0·342	98·9	100·7
33	Som.	M	51	1·54	HHD (compensated)	2·81	117·0	99·9	11·69	157·9	0·498	11·192	9·57	95·8	4·99	4·27	97·6	98·2
						0·258	74·5	103·9	7·73	53·1	0·0154	7·715	10·36	99·8	0·1482	0·198	99·7	100·1
34	Such.	F	31	1·53	RHD, AS, AR, LF	0·651	132·5	108·5	14·38	106·6	0·0785	14·301	10·79	99·5	0·717	0·541	99·4	100·2
						1·27	164·0	109·0	17·9	55·5	0·0798	17·820	10·88	99·6	0·732	0·446	99·2	100·2
						0·472	132·0	108·5	14·3	59·0	0·0314	14·269	10·8	99·8	0·289	0·2193	99·6	100·1
35	Soj.	M	53	1·91	HHD, LF	4·28	62·2	107·0	6·67	96·5	0·374	6·296	10·12	94·3	3·50	5·63	92·8	101·5
						1·47	35·4	103·5	3·66	75·9	0·101	3·559	10·04	97·3	0·976	2·76	95·8	101·4
						0·555	24·4	102·6	2·50	32·8	0·0165	2·483	10·18	99·4	0·1607	0·659	97·4	102·0
													Mean 10·67					

For comments see footnote to Table I. HHD = hypertensive heart disease; RHD = rheumatic heart disease; IHD = ischaemic heart disease; SHD = syphilitic heart disease; AR = aortic regurgitation; AS = aortic stenosis; MR = mitral regurgitation; MS = mitral stenosis; LF = left ventricular failure; RF = right ventricular failure.

in normal subjects (Table I and Fig. 1). Accordingly, with a low chloride filtration, the excretion of chlorides was also very low, falling to 0·01 mEq per minute in Cases 29, 30, 31, and 35 when the glomerular filtration was about 35 ml. per minute or less.

A spontaneous change in the output of urine was observed in 16 of these 25 patients. In Case 11 this increase of urine flow was accompanied by an increase in the inulin clearance slightly exceeding that observed in the chloride clearance, so that the chloride/inulin clearance ratio (column *q*) fell by about 10 per cent. In Case 34 the excretion of chlorides differed insignificantly between a period of low urine flow and the subsequent period of diuresis. The onset of diuresis in this patient was associated with an increase in the rate of glomerular filtration and a fall in the chloride/inulin clearance ratio. But during the last part of the experiment her output of urine fell to an average value of 0·472 ml. per minute, and there was a concomitant drop both in the chloride output and in the chloride/inulin clearance ratio. Her diuresis occurred shortly after supper, and the behaviour of the chlorides in this part of the experiment resembled that observed in Case 7 (Table I). The behaviour of the chloride clearance and of the chloride/inulin clearance ratio in the second part of this experiment is characteristic of that encountered in the remaining 14 cardiac patients in whom a change in diuresis was observed.

Fig. 2 demonstrates that when the output of urine was low the chloride clearance varied as a direct function of the inulin clearance, the chloride/inulin clearance ratio thus remaining unchanged, but that in most of our subjects a sharp rise in chloride output accompanied the onset of diuresis. The increase of chloride clearance thus produced is out of all proportion to the increase in the rate of glomerular filtration. In one patient (Scho.) whose inulin concentration index fell to 16, indicating that up to 8 per cent. of the glomerular filtrate escaped reabsorption, over 10 per cent. of the filtered chloride was excreted. Only four subjects reacted differently, their chloride/inulin clearance ratio remaining practically unaltered over a wide range of changes in urine flow and water reabsorption. In the patient Ště. (Case 7, Table I) this difference has already been attributed to water diuresis. The same was probably true of the patient Vac. (Case 8, Table I) in whom the urine flow increased about one hour after her evening meal, which consisted of oatmeal and half a pint of fruit juice. But there was a slight increase in the chloride/inulin clearance ratio at the peak of her diuresis, when the inulin concentration index fell to 40. A slight but definite increase in the chloride/inulin clearance ratio also occurred when the inulin concentration index was low in the patient Get. (Case 27, Table II) who had a high urine flow throughout the course of the observation. Her glomerular filtration averaged 131·2 ml. per minute, yet her chloride clearance was lower than that usually found in subjects with a similar rate of glomerular filtration and diuresis. In this respect she resembled our normal subject Ště. (Case 7, Table I) who had a water diuresis. The fourth exception was the patient Voj. (Case 11, Table II) mentioned above, who suffered from syphilitic aortitis; she was highly emotional, and had several attacks of angina

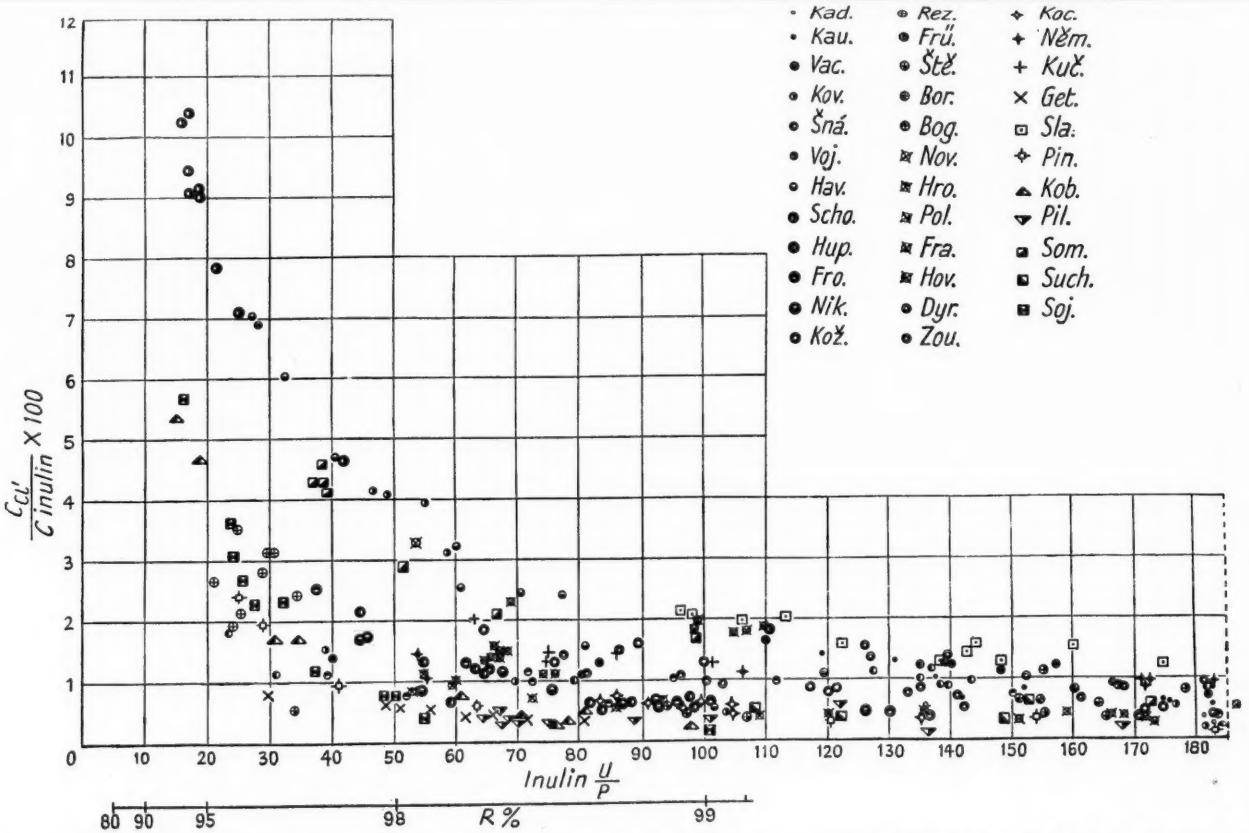

FIG. 2. Relationship between the chloride/inulin clearance ratio and the inulin concentration index (U/P). R indicates the quantity of water reabsorbed in the tubules from the glomerular filtrate. In the patients Voj., Get., Vac., and Ště., the clearance ratio did not change with a falling concentration index. In all the other subjects the clearance ratio markedly increased whenever inulin U/P fell below 80.

pectoris in the course of the observation, so that no conclusions can be drawn from the data obtained. A water diuresis was also observed in the patient Such. (Case 34, Table II) to whom we have already referred; but her lowest inulin concentration index was 108 (Fig. 2), well above the limit below which we found diuresis to be accompanied by a rise of the chloride/inulin clearance ratio.

TABLE III

Chloride Output with an equal Tubular Chloride Load and Changing Urine Flow, in Normal Subjects

Case number	*Patient*	*Diagnosis*	*Plasma-chlorides* (P_{Cl}) (*mEq/1,000 ml.*)	*Glomerular filtration* ($C_{inul.}$) (*ml./min.*)	*Tubular chloride load* ($P_{Cl} \times C_{inul.}$) (*mEq/min.*)	*Urine flow* (V) (*ml./min.*)	*Chloride output* ($U_{Cl} \times V$) (*mEq/min.*)
4	Fra.	Convalescent pneumonia	110·3	123·5	13·65	2·31	0·446
			110·5	122·1	13·5	1·24	0·246
7	Ště.	Normal	107·5	116·0	12·45	3·42	0·0678
			109·0	114·5	12·5	0·48	0·0311
8	Vac.	Normal	103·0	125·5	12·9	0·80	0·1595
			103·0	125·5	12·93	1·51	0·167
			103·0	113·2	11·68	2·83	0·163
			103·0	115·5	11·90	0·758	0·130
9	Kov.	Normal	101·4	97·2	9·86	1·76	0·3825
			98·7	97·0	9·66	0·55	0·0547
			101·3	100·5	10·2	2·14	0·418
			100·0	101·2	10·1	0·98	0·047
10	Šna.	Normal	104·0	84·4	8·74	3·64	0·1571
			102·0	85·0	8·76	0·62	0·1075

The data refer to individual observation periods. They are not reduced to an ideal body-surface area.

The marked rise both in chloride excretion and in the chloride/inulin clearance ratio, when the output of urine is high, may be due to two different mechanisms. It may be analogous to the behaviour of glucose and vitamin C, which appear in the urine when the maximum reabsorptive capacity of the tubules (Tm) for these substances is passed. In this case we should expect that the chloride output of an individual patient at a given rate of glomerular filtration (the plasma-chloride level being nearly constant) would be the same irrespective of the urine flow. Even allowing for individual variations of the postulated $Tm_{Cl'}$, we should expect from an analogy with the maximum tubular reabsorptive capacity (Tm) for other substances that $Tm_{Cl'}$ would be relatively constant in normal subjects. Consequently the range of variations of chloride output ($U_{Cl'}.V$) in various subjects at a given tubular chloride load ($P_{Cl'}.C_{inul.}$) should be rather narrow. The alternative mechanism by which chloride excretion might be enhanced at a high urine flow is the flushing out of chlorides from the tubules by water which has escaped reabsorption. In Table III we have

summarized seven comparative tests, made in five normal subjects, of the chloride output during periods of high and low urine flow but of nearly constant tubular chloride load ($P_{Cl'}.C_{inul.}$) in each individual. In Cases 4, 7, 9, and 10 the chloride output was markedly higher at high than at low urine flows, and

TABLE IV

Chloride Output with an equal Tubular Chloride Load and Changing Urine Flow, in Patients with Heart Disease

Case number	*Patient*	*Diagnosis*	*Plasma-chlorides ($P_{Cl'}$) (mEq/1,000 ml.)*	*Glomerular filtration ($C_{inul.}$) (ml./min.)*	*Tubular chloride load ($P_{Cl'} \times C_{inul.}$) (mEq/min.)*	*Urine flow (V) (ml./min.)*	*Chloride output ($U_{Cl'} \times V$) (mEq/min.)*
11	Voj.	SHD, AR, LF	116·5	71·3	8·7	1·82	0·094
			116·5	73·0	8·9	0·86	0·082
			116·6	73·6	9·02	1·00	0·091
			116·0	71·5	8·75	0·63	0·061
12	Hav.	HHD, emphysema, chronic bronchitis, RF	123·0	67·5	8·3	0·95	0·205
			119·0	73·2	8·7	2·6	0·606
13	Scho.	IHD, LF, RF	107·0	52·1	5·57	0·472	0·102
			101·0	54·5	5·5	3·17	0·603
16	Fro.	IHD, LF, RF	107·8	65·3	7·05	1·74	0·178
			107·8	65·0	7·02	1·05	0·092
21	Kož.	IHD, RF	120·4	87·8	10·5	0·73	0·083
			120·4	89·0	10·7	1·38	0·162
24	Něm.	RHD, MR (compensated)	111·5	101·9	11·35	1·89	0·169
			113·0	100·0	11·3	0·506	0·100
28	Sla.	RHD, AR, LF±	106·0	128·5	13·6	0·932	0·181
			102·0	133·5	13·57	1·384	0·288
30	Pin.	IHD, LF, RF	119·5	41·3	4·94	0·210	0·009
			120·5	39·7	4·78	0·965	0·047
32	Pil.	IHD, LF, RF	91·8	88·4	8·2	0·296	0·005
			95·0	88·8	8·4	1·00	0·039
33	Som.	HHD (compensated)	99·3	130·5	12·95	3·39	0·556
			101·0	128·0	12·92	0·734	0·077
34	Such.	RHD, AR, AS, LF	109·0	138·0	15·05	1·28	0·076
			108·8	136·8	14·9	0·63	0·044
35	Soj.	HHD, LF	102·0	40·3	4·12	1·465	0·093
			103·0	43·0	4·3	0·423	0·0117

The data refer to individual observation periods. They are not reduced to an ideal body-surface area. HHD, hypertensive heart disease; RHD, rheumatic heart disease; IHD, ischaemic heart disease; SHD, syphilitic heart disease; AR, aortic regurgitation; AS, aortic stenosis; MR, mitral regurgitation; LF, left ventricular failure; RF, right ventricular failure.

in Case 4 it varied directly with the output of urine. In Cases 7 and 10 the change of chloride output was significant, although less than that of urine flow, while in Case 9 it exceeded that of urine flow. In Case 8 alone the chloride

excretion remained nearly constant in spite of a marked change in the output of urine. An analogous comparison of the data in 12 cardiac patients (Table IV) reveals that, at an individually constant filtration of chlorides, every change of urine volume was accompanied by a significant change in the chloride output, the two being proportionate in eight cases. Only Case 11 resembled the normal subject Vac. (Case 8) in showing a marked change in urine volume without any concomitant change in chloride excretion. These observations show that in the majority of subjects, at a given chloride load, the chloride output can vary widely as a function of the rate of urine flow.

Discussion

The observations of Mokotoff, Ross, and Leiter (1948) on the elimination of sodium demonstrate that there is no essential difference between the renal excretion of this electrolyte in normal people and that occurring in patients with congestive heart failure. The proportion of sodium reabsorbed from the tubular urine remaining constant and almost complete at any level of glomerular filtration, a very low sodium output will result when glomerular filtration is reduced. It follows from our experiments that a similar constant relationship exists between the rates of glomerular chloride filtration and of chloride reabsorption. Some 99·5 per cent. of the filtered chloride is reabsorbed both in normal and in cardiac subjects. It is obvious that with this very minute amount of chloride escaping tubular reabsorption, slight variations in total chloride reabsorption will result in very marked variations in the chloride output, and consequently in the chloride clearance. A slight increase in the total reabsorption of chlorides was observed in Cases 3, 6, 8, 9, and 10 (Table I) when their urine output and glomerular filtration decreased. The result was a very marked reduction in the chloride clearance, out of all proportion to the decrease in glomerular filtration. The course of events was different in Case 7: here a marked change in urine flow and in glomerular filtration was unaccompanied by any change in chloride excretion. In this patient an increase in the tubular reabsorption of chloride coincided with an increase in the tubular chloride load. Thus we observed two different types of spontaneous diuresis in normal subjects. One type was unaccompanied by an increase in chloride output, and resembled the response to a large ingestion of water, or of any hypotonic fluid which upsets the osmotic equilibrium of the *milieu interne*. That this was, in fact, a true water diuresis is suggested by its time-incidence, about half an hour after a meal which contained over 500 ml. of fluid. The other type was a diuresis which occurred during the day and receded at night. This spontaneous nocturnal decrease of urine flow was always accompanied by a fall in chloride output and in chloride clearance. The higher output of water and chloride during the day could not be traced to any particular intake of fluid or to any changes in the plasma-chloride level. This type of diuresis in our opinion is the expression of a normal 24-hour rhythm in the water and salt exchanges of the body.

Spontaneous diuresis in our cardiac patients resembled, in all cases but one,

this second type of diuresis in normal subjects in being always associated with an increase of chloride output and chloride clearance. But contrary to the rule in normal subjects, it usually occurred at night. The one exception was Case 34 (Table II); in this patient an increase of the urine flow from 0·65 to 1·27 ml. per minute led to an insignificant increase of chloride output, so that during the diuretic period the reabsorption of chlorides was enhanced. However, a subsequent diminution of the flow of urine was accompanied by a marked fall of chloride output, and thus conformed to the pattern met in the remaining cardiac patients. It is evident that the spontaneous increase of urine flow in patients with heart failure has a mechanism quite different from that of water diuresis. In the latter condition an excess of water is eliminated without any accompanying electrolytes, while the spontaneous diuresis of cardiac patients is accompanied by an increased chloride excretion. This enhanced chloride excretion was noticed by Mainzer and Hersch (1935), and occurs without any significant increase in the plasma-chlorides. The explanation which suggests itself is that this diuresis is due to the elimination of accumulated surplus tissue-fluid which, of course, contains salt as well as water. This explanation would be in accordance with the view of Popper and Brod (1938) that nocturia in cardiac disease is due to an improvement of the blood-supply to the tissues at night, and to a nocturnal tide of fluid from the tissues to the kidneys. In experiments reported in the preceding paper we showed that the primary factor in the nocturia of cardiac disease is an increased nocturnal renal blood-flow, thus confirming a suggestion made by Quincke (1893). This improved renal circulation produces an increase in glomerular filtration, with a simultaneous diminution of the tubular reabsorption of water.

The question still to be answered is how this change of renal activity accounts for the increased elimination of chlorides, and what mechanism underlies the low excretion of electrolytes in the phase of diminished renal blood-flow and oliguria. The experimental evidence of recent years (Pitts and Lotspeich, 1946; Lotspeich, Swan, and Pitts, 1947) led Wesson and Anslow (1948) and Wesson, Anslow, and Smith (1948) to the conclusion that sodium and chlorides are reabsorbed by two mechanisms, operating at different sites in the renal tubules.

1. In the proximal tubules sodium and chlorides are reabsorbed in such a way that about 85 per cent. of these electrolytes disappears from the tubular urine before it reaches the distal tubules, irrespective of the rate of glomerular filtration. Water passively follows the reabsorbed sodium and chlorides, especially in the loop of Henle, the thin epithelium of which offers almost ideal conditions for the osmotic equilibration of tubular urine and plasma. This process produces the impression of isosmotic reabsorption.

2. The reabsorption of the remaining 15 per cent. of sodium and chlorides is limited by a fixed maximal rate at which the distal tubular cells can extract these electrolytes ($Tm^d_{Cl'}$ and Tm^d_{Na}.). At a fixed rate of glomerular filtration, whenever the plasma-chloride or -sodium exceeds a certain value, more chloride or sodium will be delivered to the distal tubule than can be reabsorbed, and the amount of the electrolyte excreted will suddenly increase. The same is true if,

instead of a change in the level of chloride or sodium in the plasma, the plasma concentration remains fixed and the rate of glomerular filtration changes—a condition which more nearly represents the variations occurring physiologically. Wesson, Anslow, and Smith (1948) drew the logical conclusion that there is only one critical level of glomerular filtration at which electrolytes are neither accumulated nor lost by the body.

Our data in Fig. 1 are in agreement with the first part of this hypothesis; they reveal that the proportion of chlorides reabsorbed from the glomerular filtrate remains roughly constant, irrespective of the rate of glomerular filtration. Consequently the chloride load in any part of the tubules will increase in direct ratio to an increase in the rate of glomerular filtration. Should the distal tubular reabsorption of chlorides be limited by a certain $Tm^d_{Cl'}$, as the second part of the hypothesis (Wesson and Anslow, 1948; Wesson, Anslow, and Smith, 1948) suggests, it would follow that up to a certain point the elimination of chlorides would be practically nil, and that a sharp increase would suddenly follow any further rise in the rate of glomerular filtration. This conclusion seems to be borne out by the data shown in Fig. 2. This distal threshold seems to be individual and to vary from one subject to another. Thus in one normal subject (Case 4, Table I) a high chloride excretion was present with a tubular load of 12·8 milliequivalents per minute, while in Case 3 a similar chloride load resulted in a chloride output about one-tenth of that found in Case 4. There was no obvious correlation between this renal threshold for chlorides and the plasma-chloride level, as can be seen from Table I. On the other hand, a chloride excretion similar to that in Case 4 occurred in a heart patient (Case 31, Table II) with a tubular load of only 3·78 milliequivalents, and more than twice the quantity of chloride was excreted by patient Scho. (Case 13, Table II) with a tubular load of 6·51 milliequivalents. If a $Tm^d_{Cl'}$ exists it must therefore vary widely in different individuals, and must in general be lower in cardiac than in normal subjects. But the data shown in Tables III and IV cannot be reconciled with the idea of a fixed $Tm^d_{Cl'}$. It is obvious that at a given tubular chloride load the chloride excretion and chloride clearance varied with the rate of the urine flow, and we can also understand why subjects with such widely divergent tubular chloride loads as Case 4 (Table I) and Case 31 (Table II) may have comparable chloride clearances. The rate of glomerular filtration in decompensated cardiac disease is far below normal. Its increase to low normal values (80 to 100 ml. per minute) is usually accompanied by a marked rise of urine flow. In normal subjects glomerular filtration frequently drops to this low normal level at night, when their urine flow is low. The chloride content of the plasma is the same in both groups. Consequently when the rate of glomerular filtration is the same in both, the tubular chloride load must be equal. *Yet these cardiac patients with diuresis excrete substantially more chlorides than normal subjects who have a low urine flow.* The difference in urine flow between decompensated and compensated cardiac patients, which we have shown to be due to changes in renal blood-flow, will also satisfactorily explain the difference between the sodium clearances of these two classes of heart patients which was recently

found by Briggs, Fowell, Hamilton, Remington, Wheeler, and Winslow (1948); these authors attributed the low sodium clearance of decompensated cardiac patients to hypoxia.

Our results are compatible with the theory that when the glomerular filtrate reaches the distal tubules the greater part of the chlorides has already been reabsorbed. Whatever might be the fate of the small fraction left in these tubules, the impression would remain of a constant relationship between tubular load and total tubular reabsorption of chlorides. Our data show a wider scatter than those of Mokotoff, Ross, and Leiter (1948) owing, no doubt, to the fact that these authors carried out their experiments at periods of normal or very high urine flow, whereas our data were collected from observations on cardiac patients which extended over many hours, during which their urine flow varied from very low to normal. The fate of the remaining chlorides depends not only on the capacity of the distal tubular cells to reabsorb them, but also on the time left for contact between the distal tubular fluid and the tubular cells. This time becomes shorter with increased diuresis, so that less chloride will be reabsorbed. Thus at higher urine flows the chloride clearance will increase out of all proportion to the increased rate of glomerular filtration. When, on the contrary, with the decline of renal blood-flow, glomerular filtration decreases and tubular reabsorption of water is at its height, sufficient time is left for an almost complete reabsorption of the small residue of the already diminished tubular chloride load. This abnormal mechanism is present already in the early stages of heart failure. Compensation is provided, as shown in the preceding paper, by a high electrolyte output during the night's rest. With the progress of decompensation the nocturnal tide of blood to the kidneys diminishes, and finally ceases altogether. The abnormally high electrolyte reabsorption becomes permanent, and results in the marked accumulation of electrolytes and fluid in the body which is characteristic of the late stages of cardiac decompensation.

The question whether nocturia passively follows an increased chloride output, due to an active depression of chloride reabsorption during rest, must be answered in the negative. In only six instances was the urinary chloride concentration higher than the chloride content of the plasma, suggesting that distal portions of the tubules were relatively impermeable for chlorides, while water was still being withdrawn. These distal portions are probably very short, so that the chloride U/P ratio never exceeds two. In the majority of instances the chloride concentration in the urine of our patients was below that found in the plasma. It therefore seems more likely that a rapid evacuation of urine from the distal tubule interferes with the distal reabsorption of chlorides. The fact that the chloride U/P ratio is usually less than one shows that the distal tubules do reabsorb chlorides, if we accept existing evidence that, under physiological conditions, the fluid at the beginning of the distal tubules is isosmotic with the plasma (Walker, Bott, Oliver, and MacDowell, 1941). The mechanism by which a high urine flow interferes with the completeness of the distal tubular reabsorption of chlorides is not quite clear. Mayer and Rathery (1928) observed that in rabbits the tubules are dilated during diuresis. If tubular dilatation

accompanies an increased flow of urine, it may result in the incomplete reabsorption of dissolved substances from the axial stream in the distal tubules.

The investigation was made with the help of grants from Czechoslovak United Pharmaceutical Industries and the Ella Sachs Plotz Foundation, Boston, U.S.A.

Summary and Conclusions

1. The chloride excretion during spontaneous nocturnal changes of urine flow was studied in 10 normal and 25 cardiac subjects, 19 of whom were in a state of heart failure.

2. Tubular reabsorption was very high in both groups, accounting for about 99 to 99·5 per cent. of the filtered fluid irrespective of the rate of glomerular filtration, and producing the impression of a constant rate of reabsorption for every 100 ml. of glomerular filtrate.

3. In one normal subject the flow of urine increased without any change in the chloride output. As this diuresis was accompanied by a definite increase in glomerular filtration, the unchanged chloruresis must have been due to an enhanced reabsorption of chlorides. Evidence is brought forward for the belief that the diuresis was due to a previous intake of fluid.

4. In all cardiac patients but one the chloride output markedly increased with diuresis. This increase was out of proportion to the simultaneous increase of glomerular filtration and of tubular chloride load. Even when the excretion of urine and of chlorides was high in cardiac patients, their chloride load was usually far below that found in normal subjects with a similar degree of diuresis and of chloride output.

5. With the same tubular chloride load marked differences in chloride excretion were observed, and followed the rate of urine flow.

6. The very low output of chlorides, and possibly of sodium, in cardiac patients with failure is the result of a diminished tubular chloride and sodium load and an almost complete reabsorption of these filtered electrolytes, made possible by a low urine flow.

7. The mechanism of the renal excretion of chlorides is discussed, and it is suggested that the increase in chloride excretion in cardiac patients during nocturia is produced by a diminished distal tubular chloride reabsorption, due to a shorter contact of the chloride with the reabsorbing tubular cells.

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616.16–007.64:616.24

TELANGIECTASIS OF THE LUNGS[1]

WITH TWO CASE REPORTS OF HEREDITARY HAEMORRHAGIC TELANGIECTASIA WITH CYANOSIS

By A. J. BRINK

(From the Department of Systematic Medicine, University of Pretoria)

With Plate 16

Cyanosis resulting from generalized telangiectasia has been recorded in surprisingly few instances in the available literature. Until recently only two such cases had been reported, and in both the discoloration was attributed to peripheral vascular factors (Constam and Brown, 1928; McDonough, Dry, and Roth, 1940). The association of pulmonary arteriovenous shunts with angiomatosis in other sites has occasionally been noted, but it was not until 1947 that Whitaker suggested that the pulmonary lesion was but another manifestation of hereditary telangiectasia. This suggestion was convincingly confirmed by Hayward and Reid (1949) and by Yater, Finnegan, and Giffin (1949) in reviews of the published cases and reports of their own observations.

The diagnostic criteria of hereditary haemorrhagic telangiectasia have been so well described by Osler (1901) and Weber (1907), and later by Goldstein (1931) and Cappon (1945), that the triad of telangiectasia, haemorrhage, and a familial history should offer no diagnostic problem. The factor of heredity, although fairly well established as the most important cause (Steiner, 1917) is not essential to the diagnosis, since there seems to be little doubt that the disease exhibits atavism (Fitz-Hugh, 1923). Its relationship to other vascular anomalies, and to associated morbid conditions such as lesions of the liver and deficiency diseases, has been adequately discussed by Williams and Snell (1938), Bean (1945), and Weber (1946). Many organs are known to become involved in hereditary telangiectasia. It is these unusual visceral manifestations that have attracted most interest (Schuster, 1937; McDonough, Dry, and Roth, 1940; Penfold and Lipscomb, 1943; Rundles, 1945; Kushlan, 1946). The following report and discussion are concerned mainly with the production of cyanosis in telangiectasia. Other features of the first case to be described are rarely found in association with telangiectasia: these are recurrent haematuria, a tendency to haemolysis, a hepatic angioma, and an enlarged spleen.

A full appreciation of the cases to be reported demands a brief discussion of the factors which contribute to the production of cyanosis. They may be classified as follows.

1. Peripheral vascular factors. (*a*) Arteriolar spasm, resulting in a slowing of the circulation through the cutaneous capillaries and venules, with a greater

[1] Received January 26, 1950.

degree of oxygen unsaturation in their contained blood; e.g. acrocyanosis and Raynaud's syndrome. (*b*) Slowing of the venous flow from factors such as cardiac failure, again with an increased amount of reduced haemoglobin in the peripheral circulation. (*c*) Increased visibility of the capillary and venous network.

2. Central factors. (*a*) An insufficiency of the blood reaching the pulmonary alveoli and receiving oxygen. (i) Congenital heart disease such as pulmonary stenosis, septal defects, or overriding aorta. These conditions are accompanied by a shunting of blood from the venous to the arterial side. (ii) Pulmonary abnormalities, such as communications between the pulmonary artery and vein, or an altered alveolar or capillary permeabilty to oxygen. The latter condition is found, for example, in Eisenmenger's complex and in obliterative pulmonary vascular disease. (iii) Polycythaemia, with inadequate exposure of the red cells to the alveolar epithelium. (*b*) Altered respiratory mechanics leading to a lowering of oxygen-tension in the alveoli. This may be the result of disease, such as emphysema, or of external conditions, such as high altitudes.

3. Abnormal blood-pigments, as in methaemoglobinaemia or sulphaemoglobinaemia.

Capillary blood needs an oxygen unsaturation of six to seven volumes per cent., or five gm. of reduced haemoglobin per 100 ml. of blood, for cyanosis to become clinically evident. The depth of the cyanosis may be greatly modified by the thickness of the skin, by the pigment-content of the skin, by the colour of the blood-plasma, and by the quantity of capillary blood exposed in the skin. The last factor is determined by the number, width, and length of the blood-filled capillaries and venules (Brown and Sheard, 1926).

Case Reports

Case 1. A European married woman aged 19 years was admitted to hospital on February 10, 1949, for a small epigastric hernia, which was said to have been present for five years. At operation the contents were discovered to be a pulsating haemangiomatous mass extending into the liver substance along the falciform ligament. The hernia was closed, and the patient was referred for further investigation. In 1945 she had had pyrexia and coughed blood in small quantities, and this episode was termed 'pneumonia'. Since then she had had frequent small haemoptyses. Epistaxis had developed during the same year and had recurred many times since, being so severe on two occasions as to necessitate medical treatment. Towards the end of 1946 a blue discoloration of her fingertips, toes, and lips was first noticed. In later months she had noticed a rounding off of her fingers. A diagnosis of inflammation of the kidneys had been made in 1947 when she saw blood in her urine. No change had been found in her exercise-tolerance, though she was thought in 1947 to have slight oedema of her ankles. Menstruation had not yet commenced at the time of her admission. A report of frequent sore throats, poor appetite, and loss of weight completed her personal history. Neither the patient nor her mother knew of any familial tendency to haemorrhage. Her father's relatives were not known to the remaining members of the family; he had died many years before. She was one of six children. Two sisters younger than the patient were available for inspection. They both had a few punctate angiomata on the arms and hands, similar to several of those seen on the patient. One of these sisters, 17 years of age, admitted to frequent nose bleeding.

During a period of 10 months the patient was admitted three times, February 10, 1949, May 3, 1949, and October 11, 1949, and each time she had a temperature of 101° F. and a small haemoptysis. No evidence of respiratory infection could be found on these occasions, but she responded each time to penicillin injections within two days of their commencement. The symptoms had definitely progressed in the intervals; cyanosis had increased, and breathlessness had become a prominent feature. Haematuria developed in hospital during her second stay, lasting for four or five days and producing a rather severe clot colic. Just before her third admission bleeding occurred from an angioma situated on the tip of her left middle finger. It recurred twice in hospital, each time while she was in a hot bath. The bleeding was observed to come in spurts.

Her condition on examination remained unaltered, except for an increase in the number of angiomata and in the depth of cyanosis during the 11 months of observation. The special investigations described below were carried out at intervals during this time. She was a young, normally developed woman, with obvious cyanosis of the lips, finger-tips, and toes. The fingers and toes showed clubbing. Multiple angiomata, dusky red in colour, were present particularly on her hands, arms, and neck. Some could be seen on her thighs. The angiomata were of the 'spider' and punctate forms, and were more profuse on the right side of her body. They were absent from the trunk, except for the shoulder regions. At the time of her third admission 150 angiomata were found. The punctate angiomata in many regions were surrounded by pale ischaemic halos. Several of the larger angiomata could be felt to pulsate; in others pulsation could be seen when pressure was applied with a glass slide. The patient's hands had a purplish-blue discoloration, more marked over the hypothenar eminences. The soles of the feet were similarly discoloured. The bluish discoloured areas could be blanched by pressure, the colour returning rapidly both from the peripheral and from the central regions of the blanched area. A striking feature was the moist warmth of the hands. This, together with the rapid central filling of the blanched areas, suggested that there was no arteriolar spasm of the kind found in acrocyanosis. Immersion of the foot in cold water at 56° F. lowered the skin temperature of the toes from 92° F. to 82° F., and caused intensification of the cyanosis. Raising the temperature of the toes to 95° F. in water at 110° F. improved the cyanosis only slightly. Venous stasis, produced with a sphygmomanometer cuff or by arteriolar constriction with cold, aggravated the cyanosis. It appeared that warmth could not much increase the existing arteriolar dilatation and so appreciably reduce the cyanosis. Examination of the mucous membranes revealed very little. A meshwork of telangiectatic vessels was present on the soft palate, where no punctate angiomata were seen. On the mucocutaneous borders of the anterior nares two telangiectatic areas were seen, one on each side. Sigmoidoscopic and vaginal inspections revealed no vascular anomalies. The tourniquet test for capillary fragility was negative.

Clinical examination of the heart did not show any enlargement. The heart sounds were 'closed', and no murmurs were audible. Reduplication of the second pulmonary sound was present. The lungs appeared normal on percussion and auscultation. The diaphragm appeared to move well on both sides. The pulse was normal in rhythm, and there was a mild tachycardia. The blood-pressure was 115 systolic and 80 diastolic. In the abdomen the spleen was easily palpable, and no other abnormalities were detected. The retinae appeared to be normal. The patient's teeth were healthy, but on her second admission to hospital a root-abscess of the lower right first premolar made extraction necessary. No prolonged bleeding occurred after this procedure. There were no abnormal neurological signs. Analyses of the urine were normal chemically and

microscopically, except for the episode of haematuria during her second stay in hospital.

The red cells were 5,700,000 per c.mm., and haemoglobin 113 per cent. Ten months later the red cells were 6,100,000 per c.mm., and haemoglobin 117 per cent. by the Leitz colorimeter and 125 per cent. by Wong's iron method (14·6 gm. of haemoglobin being regarded as 100 per cent.). A leucopenia (2,000 to 3,000 cells per c.mm.) was recorded on several occasions. The distribution of the white cells remained about the same: polymorphonuclear neutrophil cells 48 per cent., lymphocytes 36 per cent., monocytes 10 per cent., and eosinophil cells 5 per cent. Platelets were present in normal quantities. Anisocytosis and poikylocytosis of the red cells was seen, but no elliptocytosis. Haemolysis occurred between 0·46 per cent. and 0·32 per cent. of saline. A qualitative van den Bergh test was indirectly positive on two occasions; a later quantitative estimation gave values of 1·8 mg. total serum-bilirubin and 0·4 mg. direct-reacting bilirubin per 100 ml. The presence of a haemolytic tendency was inferred. The haematocrit reading in a Wintrobe tube was 49 mm. of packed cells and 51 mm. of plasma. The sedimentation rate by the Westergren method was 10 mm. in the first hour. Two blood cultures made at an interval of four months were negative. Abnormal blood-pigments were looked for spectroscopically on two occasions, with negative results. Examinations of the serum, mainly carried out during the patient's third stay in hospital, gave the following results: prothrombin, 65 per cent. of normal; thymol turbidity ++++; serum-proteins, 6·38 gm. per 100 ml. (albumin 4·05 gm., globulin 2·33 gm., albumin/globulin ratio 1·73: 1); alkaline phosphatase, 29·6 King and Armstrong units; cholesterol 150 mg. per 100 ml.; creatinine 0·55 mg. per 100 ml.; carbon dioxide combining power, 63 volumes per cent. The Wassermann reaction was negative. The patient's basal metabolic rate was +4 per cent.

Congenital heart disease had to be considered, and the following investigations were carried out with that condition in mind. Electrocardiographic examination with the standard leads and the six unipolar precordial, VE, VB, and unipolar limb leads demonstrated only some left axis deviation, with the heart in the horizontal position. Radiological examination of the chest showed no enlargement of any of the cardiac chambers in either the antero-posterior or the oblique views. The position and shape of the heart appeared normal. The lungs seemed to be unusually vascular. Angiocardiography showed the presence of the dye after one second in the superior vena cava, right auricle, right ventricle, pulmonary artery, and proximal pulmonary arterial branches. The absence of the dye in the aorta at this stage seemed to exclude the possibility of Eisenmenger's complex and, together with the easy demonstration of the pulmonary artery, was against the diagnosis of Fallot's tetralogy. The circulation time from arm to tongue, measured by the use of five ml. of 10 per cent. magnesium sulphate solution, was eight seconds, and from arm to lung, measured with 0·33 ml. ether and 0·33 ml. normal saline, three and a half seconds. Blood samples were taken from the superior vena cava, the right auricle and the right ventricle with a cardiac catheter, and arterial blood from the femoral artery. Pressure measurements could not be made owing to lack of the necessary apparatus. Gas analyses by the manometric Van Slyke technique yielded the following results:

oxygen capacity . . .	21·2	volumes	per cent.
oxygen content, femoral artery .	17·0	,,	,,
,, ,, superior vena cava	13·0	,,	,,
,, ,, right auricle .	12·65	,,	,,
,, ,, right ventricle .	12·10	,,	,,

From these values it appeared that there was not much likelihood of a septal defect of the heart, since they did not indicate a shunting of blood from left to right. During catheterization the catheter was at no time seen to enter the left side of the heart. It could not be passed into the pulmonary artery. The recorded oxygen capacity and oxygen content are affected by the consideration that blood, at our altitude, may be only 92 to 93 per cent. saturable with oxygen (Stammers, 1933).

This patient's cyanosis was completely relieved by the administration of oxygen, but only in the earlier months of observation. Later, cyanosis was relieved but not removed. A pulmonary factor of a progressive kind was therefore considered to be the cause of oxygen-unsaturation in her arterial blood. This pulmonary factor made it impossible to use the direct Fick principle in calculating the cardiac output, or to make use of the formulae of Bing, Vandam, and Gray (1947), these principles being based on the assumption that pulmonary venous blood is approximately 95 per cent. saturated. A progression in the patient's disease became evident from the increased number of angiomata, the greater depth of cyanosis, dyspnoea even when at rest, and the failure of oxygen administration to relieve cyanosis, and was confirmed by repeated oxygen determinations in her blood, which were carried out five months after the first test with the following results:

oxygen capacity . . .	21·2	volumes per cent.
oxygen content, femoral artery	15·0	,, ,,
,, ,, brachial vein	13·2	,, ,,

After a brisk walk the oxygen in her venous blood was 8·1 volumes per cent. Her feet had appeared to become larger since her previous admission to hospital, and she stated that it had become necessary to wear a larger size of shoes. Radiological examination of her feet demonstrated an increased density of the cortex of both the fifth metatarsals, a result which was thought compatible with the diagnosis of hypertrophic pulmonary osteo-arthropathy. No angiomatous infiltrations of the skull or vertebrae could be found by X-rays. In March 1950 this patient had an upper intestinal haemorrhage, and was admitted to hospital for the fourth time.

Comment. Of the several remarkable features present in this case, the cyanosis demands particular emphasis. Congenital heart disease was satisfactorily excluded both by the clinical evidence and by the radiological, electrocardiographic, and angio-cardiographic investigations and the limited data obtained by cardiac catheterization. Positive evidence of a central causative factor was given by the oxygen-unsaturation values. A pulmonary cause was clearly indicated by the relief of cyanosis when oxygen was administered early in the period of observation. An explanation was sought in the associated telangiectases. The frequent haemoptyses suggested their presence in the lungs. The only possible explanation seemed to be that these vascular lesions had led to the formation of small pulmonary arteriovenous fistulae, which were shunting a portion of venous blood directly to the arterial side. This hypothesis is strengthened by a consideration of Case 2, and of other factors affecting the normal and abnormal pulmonary circulation which are to be taken up in the discussion.

The mean unsaturation of the capillary blood calculated from the first determinations amounted to six volumes of oxygen per cent. Subsequent estimations showed an increase to 6·8 volumes, and to 9·5 volumes after exercise. Clinically the cyanosis was much more evident than the determinations of oxygen-unsaturation would suggest. The possible part played by peripheral vascular factors was considered, but their nature was not obvious. The warmth of the

limbs, the small arteriovenous oxygen difference, the circulation times, and the character of the circulation in the discoloured palms and soles all suggested arteriolar dilatation and a rapid circulation. Venous stasis could not account for the depth of the colour. As in the case of Constam and Brown (1928) and in that of McDonough, Dry, and Roth (1940), the explanation must lie in a greater visibility of the subcutaneous capillaries and venules, exposing to view a greater amount of venous blood. The haemolytic tendency may have been associated with the splenomegaly, the two constituting an additional inherited factor. Haemolysis has previously been recorded in this disorder, but associated with elliptocytosis which was not present in this case (Penfold and Lipscomb, 1943). Alternatively, splenic enlargement might be explained by the presence of the pulsating angiomatous mass extending along the ligamentum teres into the liver. The pulsations suggested an arteriovenous anastomosis, which may have been the cause of portal hypertension with splenomegaly.

Haematuria has not often been described in classical cases of the Rendu–Osler–Weber syndrome.

Case 2. A European married woman aged 56 years was admitted on May 23, 1949. Breathlessness on exertion and attacks of nocturnal dyspnoea had commenced three months before. An attack of severe breathlessness and a haemoptysis, occurring two days before, were the cause of her admission to hospital. Apart from malaria and typhoid in childhood she had had no other illness. She had had four children, one of whom died of whooping-cough at the age of 10 months. All her pregnancies had been normal. The menses had been normal and regular, and the menopause had occurred at 45 years. Epistaxis had been frequent since her 19th year, and had become almost an ordinary experience. Her father also had suffered from frequent nose bleeding. There was no other relevant family history.

On examination she was an elderly woman of short stature, with a well-developed pigmentation of the skin. When admitted she had severe dyspnoea and was very cyanotic. There was clubbing of the fingers and toes. A rapid and grossly irregular pulse made it difficult to measure the blood-pressure, which was recorded as 180 systolic and 110 diastolic. Telangiectases, with a few punctate agiomata between them, were seen on the malar regions. Punctate angiomata were also present on the lower lip, and three were found close to the nail of the right ring finger. The mucous membranes showed discrete punctate angiomata on the inner surface of the lower lip and on the inside of the right cheek. She had no teeth. A few angiectatic vessels, but no angiomata, were visible on the mucosa of the nasal septum on both sides. Examination of the vagina with a speculum, and sigmoidoscopic examination, revealed no angiomata or telangiectases. The retinae appeared normal. Engorged and pulsatile veins were clearly visible in the neck. There was no enlargement of the thyroid or other glands. The cardiac impulse could be felt in the sixth intercostal space well outside the mid-clavicular line. No enlargement of the heart could be detected to the right. There was auricular fibrillation, with a ventricular rate of 110 per minute. The heart sounds were 'closed', and no murmurs were audible. Crepitations were heard at both bases, but at this stage no other adventitious sounds were present in the lungs, which were otherwise normal on physical examination. An enlarged, tender liver was palpable in the abdomen. Slight oedema of the legs was noticed. Examination of the nervous system demonstrated no abnormalities. On her first admission to hospital she had a blocked lacrymal duct, and was for a short time under the care of the ophthalmologist.

She was observed over a period of five months, and admitted three times to

hospital. Throughout this period the cyanosis remained unaltered, though the congestive cardiac failure was easily relieved by the usual procedures. Each admission was for a similar attack of breathlessness; there was haemoptysis again on the second, but not on the third occasion. The attacks were thought to be due to repeated pulmonary emboli. A loud bruit became clearly audible the third time she was in hospital. It could be heard at the angle of the left scapula during the height of inspiration, and was continuous throughout the cardiac cycle. This patient had not noticed the cyanosis and clubbing until it was pointed out to her in hospital. The depth of cyanosis was unaffected in this case by lowering the temperature of the hand or by raising it; administration of oxygen was also without effect.

The capillary fragility test was negative. No urinary abnormalities were found at any time. The red cell count rose from 5,150,000 per c.mm., with a haemoglobin reading of 117 per cent. (14·6 gm. being taken as 100 per cent.) on her first admission to 7,200,000 per c.mm. five months later. The haemoglobin was now 134 per cent. The mean red cell diameter was 7·5μ, and the cell morphology normal. The sedimentation rate was 13 mm. after one hour by the Westergren method. The leucocytes were 5,600, 14,000, and 12,000 per c.mm. on the three respective admissions. The distribution of white cells remained unchanged: neutrophil polymorphonuclear cells 84 per cent., lymphocytes 9 per cent., monocytes 6 per cent., eosinophil cells 1 per cent. A normal number of platelets was present. The qualitative van den Bergh test was negative, and the quantitative estimation gave values of 1·0 mg. per cent. total bilirubin and 0·2 mg. per cent. direct-reacting bilirubin. Other biochemical tests gave the following results: blood-urea, 35 mg. per 100 ml.; serum-proteins, 6·97 gm. per 100 ml. (albumin 5·1 gm., globulin 1·87 gm., albumin/globulin ratio 2·72:1); thymol turbidity ++++; alkaline phosphatase 9 King and Armstrong units per 100 ml.; Wassermann reaction, negative. Electrocardiographic examination showed the presence of auricular fibrillation.

Radiological examination of the chest showed a dense tortuous mass at the left base, localized to the lower lobe (Plate 16, Fig. 1). On tomography this shadow was best seen at 11 cm. depth, where it gave the appearance of three or four discrete masses (Plate 16, Fig. 2). Another rounded paracardiac shadow was present in the right hilar region; tomograms showed this to be part of the left auricle. The tortuous mass was clearly pulsatile on screening. The cardiac shadow was enlarged, the increase in size being of the left ventricle. Five months after the first admission, X-rays showed an increase in size of the pulmonary shadow. At the same time the oesophagus showed indentation on the right anterior oblique view, suggesting left auricular enlargement. The radiological and clinical findings justified the diagnosis of a pulmonary arteriovenous fistula. Angiocardiography was not resorted to, as the patient reacted severely to estimations of the circulation times. Measured with five ml. of 10 per cent. magnesium sulphate solution, the arm-to-tongue time was 17 seconds. The arm-to-lung time was estimated as four and a half seconds with 0·33 ml. ether and 0·33 ml. physiological saline. These readings were obtained shortly after the signs of failure had been relieved. Immediately after the injection of the ether the patient became severely distressed and complained of headache. These symptoms passed off after a few seconds.

Oxygen determinations of the patient's blood by the manometric Van Slyke technique gave the following results:

oxygen capacity . . .	24·1	volumes per cent.
oxygen content, femoral artery	13·5	,, ,,
,, ,, brachial vein	9·5	,, ,,

In interpreting the oxygen capacity it has to be remembered that blood may be only 92 to 93 per cent. saturable at our altitude (Stammers, 1933).

Comment. The cyanosis in this case is satisfactorily explained by the presence of a large pulmonary arteriovenous fistula, which appeared to have increased in size in a period of five months. A loud bruit at the angle of the left scapula was clearly heard only after months of observation, although it may have been missed earlier on. The multiple angiomata, together with a history of recurrent epistaxes during most of her life, and of similar haemorrhages in one of her parents, established the diagnosis of hereditary haemorrhagic telangiectasia.

Discussion

Large arteriovenous communications in the lungs are becoming more frequently recognized, and the number of case reports is increasing (Whitaker, 1947; Crane, Lerner, and Lawrence, 1949; Yater, Finnegan, and Giffin, 1949). Up to the present time only the radiologically visible tumours have been described, although it has become clear from a study of pathological material that these tumours are only the larger counterparts of widespread telangiectases in the pulmonary tissue (Whitaker, 1947; Hayward and Reid, 1949). It seems likely that numerous smaller lesions would produce the same physiological effect as a single large communication. Case 1 showed such a generalized telangiectasia that in the absence of a demonstrable pulmonary fistula she could justifiably be considered to have multiple small arteriovenous shunts in the lesser circulation. The pulmonary lesion in Case 2 could be regarded as a more advanced stage of one of these structures.

There is a considerable weight of evidence which favours the actual and potential existence of arteriovenous communications in the lung. The histology of these angiomatous lesions as described by Patek, Post, and Victor (1940) shows that they lend themselves to the development of shunts. In some instances the angiomata resemble magnified glomus structures, the glomus being itself an arteriovenous anastomosis. In the lungs a double blood-supply, derived from the bronchial and pulmonary systems, extends as far as the respiratory bronchioles (Best and Taylor, 1945). This anatomical arrangement results in a rich network of capillaries and venules proximal to the alveolus, and may be expected to favour the development of anastomotic channels. Communications many times larger than the average lumen of a capillary have been shown to exist between the pulmonary arteries and veins of normal dogs and rabbits (Prinzmetal, Ornitz, Simkin, and Bergman, 1949). The passage of parasitic ova such as that of the schistosomes through the lungs, and the distribution of malignant metastases, are more satisfactorily explained by the normal occurrence of such channels. In a pathological process of which the most prominent feature is telangiectasia, such structures may well increase in size and number.

It is surprising that the association of cyanosis and haemorrhagic telangiectasia has not been described more frequently. The reason may be that the patients reported were too anaemic as the result of haemorrhage to show an obvious cyanosis. Determinations of arterial oxygen have not usually been made in this syndrome unless a large pulmonary fistula was suspected, so that cyanosis,

unless clinically evident, has not been discovered. It is conceivable, too, that many of these cyanotic patients have in the past been diagnosed as suffering from congenital heart disease. The clinical diagnosis of an Eisenmenger complex was made in Case 1 by several physicians.

In conclusion it is suggested that the small arteriovenous communications occurring in the lung are physiologically quiescent, but may become functionally active in disorders other than telangiectasia. The circulatory dynamics in emphysema and in fibrotic conditions of the lung are more easily explained by such a mechanism. A rise in pressure in the blood-vessels of the respiratory bronchiole would result from closure of the interalveolar capillaries. Anastomoses would then be opened, giving rise to cyanosis accompanied by a rapid circulation-time through the lungs and a high cardiac output (McMichael, 1947). This development would tend to keep the pulmonary arterial pressure low until the process of obliteration had become extensive. A rise in pulmonary arterial pressure is known to occur only in the more advanced stages of emphysema and pulmonary fibrosis (Cournand, 1947). Oxygen administration may relieve the cyanosis in the earlier stages by dilating the pulmonary capillary bed, and so diverting a greater amount of blood through the respiratory portions of the lungs.

I wish to express my gratitude to Dr. H. W. Snyman, Head of the Department of Systematic Medicine, for his advice and for permission to publish these cases; to Professor C. Brink, Head of the Department of Physiology, for granting facilities for the Van Slyke technique; and to the Department of Radiology and the Institute of Pathology for the X-ray and biochemical investigations.

Summary

1. The occurrence of cyanosis in cases of haemorrhagic telangiectasia is discussed.

2. A case of the Rendu–Osler–Weber syndrome, with cyanosis of central origin and peripheral complicating factors, is reported. Unusual visceral complications in this patient were hepatic angioma, haematuria, haemoptyses, a tendency to haemolysis, and an enlarged spleen.

3. A second case of the syndrome is described in which there was an easily demonstrable pulmonary arteriovenous fistula.

4. The relationship of cyanosis to arteriovenous shunts in the lungs in these cases, and in chronic pulmonary lesions, is discussed.

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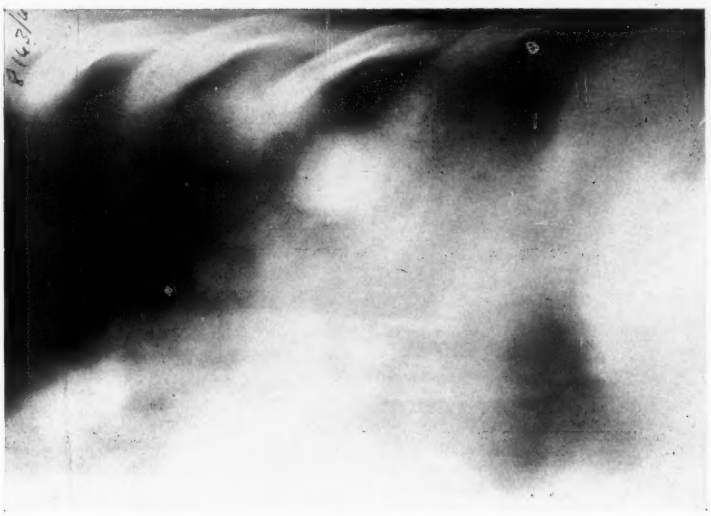

FIG. 2. Case 2. Tomogram of left lower lobe

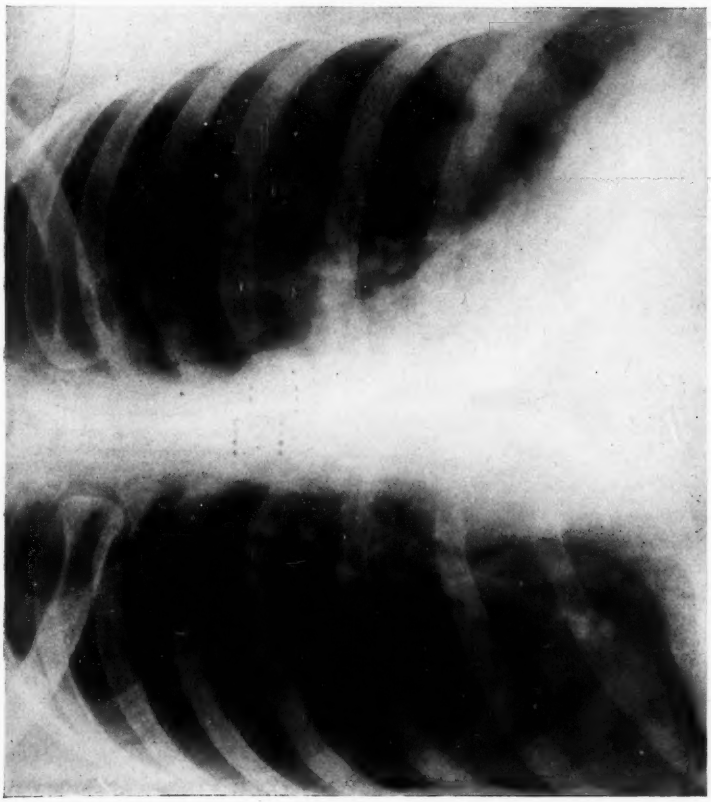

FIG. 1. Case 2. X-ray of chest during the first period in hospital

616.24–005.3

PULMONARY CHANGES DUE TO CARDIAC DISEASE WITH SPECIAL REFERENCE TO HAEMOSIDEROSIS[1]

By A. C. LENDRUM, L. D. W. SCOTT, and S. D. S. PARK

(From the Department of Pathology, The University of St. Andrews and Royal Infirmary, Dundee, and the Departments of Pathology, Medicine, and Radiology, The University of Glasgow, and the Western Infirmary, Glasgow)

(With Plates 17 to 22)

It is well known that a peculiarly mottled or vaguely nodular X-ray picture of the lungs may be seen in patients with stenosis of the mitral valve. In the earlier days of radiology, these shadows were believed to be due to congestive distension of the pulmonary vessels and to oedema of the stroma; this may possibly be so, but we have found in fact that whenever such a skiagraphic picture has been obtained during life, or from the isolated lung at *post mortem*, the lung has shown on microscopy multiple focal depositions of haemosiderin. The first appreciation of this relationship was stated by Fahr at a meeting and published later by his assistant, Rosenhagen (1928). Our observations confirm the rightness of their surmise, allow a fuller understanding of pulmonary haemosiderosis, and suggest a relationship between the different forms of exudation occurring in the lung in patients with cardiac disease.

Historical

Rosenhagen's three cases—two of mitral stenosis and one of aortic stenosis and incompetence—showed frank nodulation radiologically during life. Histologically he saw large numbers of phagocytes containing haemosiderin (referred to hereafter as siderophores) which in the first two cases were mainly in the tissues, ringing the arteries, and in the third filled groups of adjacent alveoli. Five years later Pedro Pons and Ammel Sans (1933) related similar shadows to foci of haemosiderin, as did Anglin (1938) who reported the post-mortem findings in a woman diagnosed clinically as a case of mitral stenosis with chronic miliary tuberculosis. Sosman and Weiss (1942) described the nodular skiagraphic appearances found occasionally in patients with long-standing mitral stenosis, and attributed them to collections of haemosiderin; he made no mention of the earlier workers and provided no evidence from post-mortem studies. A similar skiagraphic picture, persisting with little change for over nine years, was described by Pendergrass and Leopold (1945) in a case of mitral stenosis; they quoted a personal communication from Sosman, who had seen several such cases and had found post-mortem evidence of haemosiderin deposits. In accepting

[1] Received March 23, 1950.

these deposits as the cause of the shadows, Pendergrass and Leopold suggested that the deposits might be the end-result of perivascular interstitial haemorrhages which they believed to occur in the acute phase of the rheumatic disease. This suggestion is unacceptable to us.

Some recent workers, on the other hand, still accept pulmonary congestion as an adequate explanation of the skiagraphic nodulation, and fail to mention haemosiderin. The case described by Roch (1940) was that of a woman, thought to be tuberculous, who died after 12 years of invalidism; the necropsy revealed a congenital mitral stenosis. Two other reports, without post-mortem examination, are of particular interest in that they describe the occurrence of this nodulation in young men with *symptomless* mitral stenosis. Hurst, Bassin, and Levine (1944) found five cases of mitral stenosis with nodular pulmonary shadows in a skiagraphic examination of one and a half million recruits; of these five, one had previously been regarded as having tuberculosis, and another had suffered haemoptysis, but neither considered himself an invalid at the time of the examination. In a similar skiagraphic survey, Ryder and Reineke (1945) discovered mitral stenosis with pulmonary nodulation in an apparently healthy sailor.

The Present Study

Our interest in pulmonary haemosiderosis was aroused by a series of striking radiological findings in a patient with long-standing mitral stenosis (Scott, Park, and Lendrum, 1947). The patient was a man, aged 38 years, whose cardiac disability had followed acute rheumatic disease 11 years previously. Heart failure had been present for some years, and haemoptysis had been frequent. On admission to Professor McNee's wards in the Western Infirmary, Glasgow, the heart was found to be grossly enlarged, auricular fibrillation was present, and examination suggested stenosis with incompetence of both the mitral and the aortic valves. During his stay of some seven months in hospital, repeated skiagrams of the chest showed both the abnormal cardiac shadow of mitral stenosis and miliary shadows in the lung fields (Plate 17, Figs. 2, 3). The nodular opacities were most numerous in the mid-zones, producing there a clouded or marbled effect; towards the periphery and bases they were fewer in number, and the apices were clear. Most of the opacities were rounded, but a few were slightly elongated; they were usually one to five mm. in diameter, and occasionally larger, the majority measuring about 2 mm. The distribution, size, and opacity of the shadows scarcely changed throughout the seven months, and it was this remarkable constancy which led one of us (L.D.W.S.) to suspect that a radiologist's suggestion of miliary pulmonary congestion could scarcely be justified, and that this might in fact be a case of pulmonary haemosiderosis. The correctness of this diagnosis was eventually established at necropsy, as described below.

The frequency of skiagraphic nodulation in cases of mitral stenosis. Having seen the striking appearances in this case, we asked ourselves how often the lesser manifestations of haemosiderosis had been overlooked. A review was therefore undertaken by one of us (S.D.S.P.) of all skiagrams of the chest from

cases of mitral stenosis in the Western Infirmary during the years 1939 to 1945. None of these showed anything so obvious as our first case, although one or two were suggestive. All patients with mitral stenosis coming under our clinical observation since then have been examined for radiological evidence of haemosiderosis. Some of them showed persistent small shadows in the lung, usually confined to a single area, and ranging in character from a slight exaggeration of the normal markings to nodules which, although fewer and less dense than those in the first case, were yet unmistakably indicative of haemosiderosis. The post-mortem examination of some of these recent patients included skiagraphy of the isolated lung, either in the usual collapsed state or artificially inflated. The more precise definition of the nodules obtained in this way clearly revealed some cases which had been doubtful during life. In the film taken during life the opacities are vague in outline and distinctly larger than the actual deposits, although Gumpert (1947) apparently thought that these shadows represent the actual foci. The larger size of the shadows in the film compared with that of the foci as seen *post mortem* seemed to us explicable only by a random superimposition of the tiny deposits interrupting the traversing X-rays. To test this hypothesis, one of us (S.D.S.P.) examined superimposed wax slabs containing a random dispersion of extremely fine iron filings, and obtained skiagrams (Plate 17, Fig. 4; Scott, Park, and Lendrum, 1947) with a marbling which was reminiscent of the original clinical skiagrams. The theory that the opacities in the film are due to superimposition of tiny radio-opaque nodules in the traversed lung agrees well with the observed fact that the opacities are most obvious in the central parts, and fade away towards the periphery where a lesser thickness of lung is traversed by the rays. Incidentally, all our cases were notably free of emphysema.

Thus skiagraphy of the lungs in a series of patients with mitral stenosis will reveal a small number with easily recognizable haemosiderosis, while a further small number show less definite changes which are seen to be haemosiderosis on post-mortem skiagraphy. Lesser degrees of haemosiderosis occur, as will be described below, in which the diagnosis can be made only by visual inspection of the cut lung, or even only by microscopy.

The morbid anatomy of the lungs. Since the present investigation began, 33 cases of mitral stenosis have been studied. Five of these patients had, in addition, a well-marked stenosis of the tricuspid valve, and in these we were surprised to find no sign of haemosiderosis of the lung. Two other patients with an apparently normal tricuspid valve showed no haemosiderosis: in one of these there was no hypertrophy of the muscle of the right ventricle. The remaining 26 cases, in which abnormality of the tricuspid valve was slight or absent, all showed various degrees of focal deposition of haemosiderin (Plate 18, Fig. 5). This was at first somewhat disturbing, because the standard texts of morbid anatomy either make no mention of such foci or dismiss them as temporary deposits following the intra-alveolar rupture of varicose capillaries. Not only did we find the deposits in all 26 cases, but our study of the lungs seemed to show that such deposits are neither ephemeral nor reasonably to be explained by rupture of the alveolar capillaries.

Naked-eye examination of the pleural surface of an affected lung shows dark-bluish spots, apparently in the substance of the visceral pleura. In two oedematous lungs, where the pleural lymphatics were distended by fluid and thus clearly visible, the nodules could be seen to lie below the level, and not in the line, of the lymphatic channels. The spots are scattered haphazard, unlike those of carbon, which generally lie on the black lines of the involved lymphatics. Although the colour of the two different deposits is very similar when observed through the thin sheet of overlying pleura, on the cut surface of the lung it is often obvious that the haemosiderin nodule is dark brown, not the blue-black of carbon. In a few cases the nodules tend to be larger and more numerous in the posterior parts of the lung, but there is no obvious concentration in any particular lobe. Only three of our cases showed gross congestion, but in these, and also in a zone of lobar pneumonia, the nodules were still recognizable by the naked eye. This last observation recalls the work of Koester (1872); in describing a case of obstructive myxoma of the mitral valve with associated brown induration of the lung, he noted that the brown flecks (groups of alveoli containing pigment cells) were, if anything, more obvious in a pneumonic lobe. In cases where the carbon content of the lung is low, the nodules are easily recognizable as such, and the iron reaction shows them as a vivid blue against the buff background. The black lung of the town-dweller does not allow so confident a diagnosis with the naked eye, and the Prussian-blue reaction of the nodules is much less definite, partly because, as the microscope shows, there may be some concentration of carbon in the region of the haemosiderin focus.

Microscopically, cases of haemosiderosis differ mainly in the number of the nodules, although in our first case some of the nodules are of much larger size. At low magnification (e.g. $\times 30$) the nodules are seen to be distributed haphazard within the alveolar zones of the lung, and without any obvious relationship to the bronchi, veins, or septa (Plate 18, Fig. 6). The nodules themselves, even at this power, are seen to be groups of some four to twenty adjacent alveoli filled with haemosiderin, which with a higher power is seen to be contained within engorged siderophores. In an obvious case the foci are mostly of the larger size, with a few smaller ones due to eccentric section. Each nodule is sharply outlined by the sudden transition at its periphery; its stuffed alveoli are there bordered by air-containing alveoli, in which there are few or no siderophores. In many of the nodules the septa between the filled alveoli are thickened, whereas the walls of the air-containing alveoli are apparently normal (Plate 19, Fig. 7). The musculo-elastic tissue of the alveolar ducts is hypertrophied throughout the haemosiderotic lungs (Plate 19, Fig. 8), a finding which is not discussed further in this paper; but apart from this the normality of the pulmonary tissue between the nodules is striking, as was observed by Pedro Pons and Ammel Sans (1933) in the case which they described. The appearances in this respect make an interesting comparison with the coal-worker's lung described by Heppleston (1947), not least in the absence of any obvious emphysema around the haemosiderotic deposits. The major pulmonary arteries show, in varying degree, the usual changes seen in association with mitral stenosis and right ventricular

hypertrophy. At a slightly higher power it can be seen that the mass of haemosiderin filling the alveoli of the nodule is almost entirely contained within cells; these siderophores, the so-called heart-failure cells, are distended with haemosiderin, and are closely jammed within the filled alveoli (Plate 21, Fig. 15). Where the walls between filled alveoli are thickened they generally contain a varying amount of haemosiderin, much of which apparently lies free; in some of the nodules the septa contain traces of haemosiderin, but even where it is most obvious the amount in the stroma is small in comparison with the alveolar content.

All the other changes seem to be either the direct effect of iron on the stromal tissues or a reaction to the damage caused. The direct effect is seen firstly as a ferrous impregnation of the elastica of the small arteries. In describing iron impregnation of elastica in the lung, Bittrolff (1910), in cardiac patients, and Pilcher and Eitzen (1944), in a case of Ceelen's haemosiderosis (see below) postulated primary damage, and even rupture, of the elastica with a subsequent imbibition of iron and calcium. This suggested sequence is improbable; certainly, in any one of our cases, the ferrous impregnation was almost invariably seen in the region of the haemosiderin aggregations, and it was found only in cases with gross haemosiderosis. We feel justified in stating that in pulmonary haemosiderosis due to mitral stenosis the changes in the vascular elastica occur only where there is a local excess of iron. It is true that such impregnation frequently occurs where there are few, if any, granules of haemosiderin in the stroma, but we suggest that there is a transfer of iron in soluble form and at fairly high concentration from the store of iron in the intra-alveolar phagocytes. A similar local excess of soluble iron is almost certainly the cause of the ferrous incrustations of the splenic stroma in congenital haemolytic anaemia (acholuric jaundice) and splenic anaemia. The further effects of ferrous impregnation consist of fracture of the affected elastica with consequent giant-cell reaction, even to the extent of the development of giant-cell granulomata. These and the other finer histological changes are described elsewhere (Lendrum, 1950); suffice it to say here that distinct proliferative changes occur in relation to the foci, and that although this is obviously the lung condition described in the past as brown induration, we have found no proof of a generalized fibrosis.

The degree of congestion in the lungs of our 26 patients has been remarkably slight, and even in the case in which haemosiderosis was extreme there was almost complete absence of congestion in the alveolar capillaries. In fact, only three showed (Plate 19, Fig. 9) the congested and varicose alveolar capillaries commonly described as characteristic of the lung in cases of mitral stenosis, and in none was it present uniformly throughout the material examined. One of these three was the only case which showed, in areas without congestion of the *alveolar* capillaries, the varicose distension of the vessels in the mucosa of the small bronchi described by Orth in his text-book (1887, p. 353), by Proft (1932), and by Ferguson, Kobilak, and Deitrick (1944) in their studies of haemoptysis in cardiac disease. A further unexpected observation was the infrequency with which we could demonstrate iron either in the peribronchial lymphatics or in the

hilar lymph-nodes; indeed, in the most marked case of haemosiderosis the amount of iron demonstrable in the lymph nodes was small.

The focal nature and origin of the deposits. The intra-alveolar aggregations of siderophores, called hereafter the deposits, are certainly the result of haemorrhage into the air spaces of the lung, and since groups of *adjacent* alveoli are stuffed with siderophores, while the alveoli between the deposits are virtually free from them, the source of the haemorrhage must surely be in the respiratory

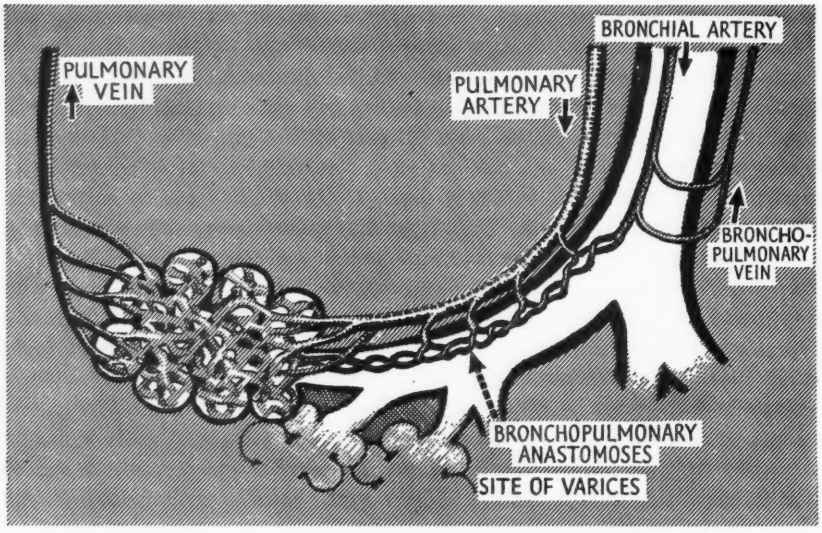

FIG. 1.

bronchiole related to the group, rather than in the alveoli themselves. It is of particular interest that a coloured plate shown by Hoyle and Orr (1945) of a section of mouse lung after intranasal instillation of a suspension of Prussian blue is almost identical in appearance with sections from our material treated with potassium ferrocyanide. The larger size of some of the deposits in our first case may indicate that the haemorrhage occurred in a larger rather than in a terminal air vessel; but a greater haemorrhage would, by reflux, invade a greater number of alveoli even if, as we imagine, the site of all the ruptures were at the same level in the terminal air passages. On the basis of microscopy alone, it appears that the haemorrhages occur in an air vessel supplying some 100 to 300 alveoli. This is approximately the anatomical region of the final sinusoidal anastomoses between the pulmonary and bronchial circulations (Fig. 1), and it is of interest that Proft (1932) and Ferguson, Kobilak, and Deitrick (1944), in their studies on pulmonary haemorrhage in chronic cardiac disease, were forced to conclude that when frank haemoptysis occurred it was from this site. Both these reports illustrated a varicose condition of the vessels in the bronchial mucosa, and Ferguson, Kobilak, and Deitrick pertinently likened the distended sinuses in the submucosa of the small bronchi to the oesophageal varices of portal

cirrhosis. By injection methods Wood, Crever, and Miller (1937) showed that in cases of mitral stenosis with right ventricular hypertrophy a gross capillary anastomosis is opened up between the pulmonary and bronchial arteries. As already mentioned, using ordinary histological methods we have only once observed distension of these sinuses in an area not showing gross distension of the alveolar capillaries. It should be remembered, however, that the histological appearances in the oesophagus from an established case of portal cirrhosis commonly fail to show the venous distension which in this disease we know exists during life. The haemodynamic disturbances accompanying the final cardiac breakdown may well remove one of the forces which were maintaining this abnormal distribution of the blood during the period of comparative health. Despite our failure to find obvious varicosity localized in the bronchial mucosa, except in one case, we believe that *the size, shape, and distribution of the deposits point definitely to the vessels of the small bronchi as the source of the haemorrhage.* Our view that the deposits could therefore be traced to haemorrhage from the broncho-pulmonary anastomoses seemed at first difficult to reconcile with the peculiar plaque-like deposits of haemosiderin found in the substance of the visceral pleura. This difficulty is resolved, and our hypothesis strengthened, by the observations of Miller (1937) that in man the capillary network of the pleura is supplied by the bronchial artery.

We are thus led the more confidently to suggest that the site of all the deposits is determined by the broncho-pulmonary anastomoses which may, during life, be in a varicose state if there is increased pressure in the pulmonary vessels. It is certain that, given an obstruction to pulmonary outflow (as in mitral stenosis) and a right ventricle capable of hypertrophy and so of raising the pulmonary intravascular pressure (which is known to occur in apparently fit patients with mitral stenosis; McMichael, 1949), the observed result is focal haemosiderosis. In the absence of hypertrophy of the right ventricle (in five cases owing to associated tricuspid stenosis, and in one for no obvious reason) we failed to find haemosiderosis. We consider that all the evidence points to a mechanical causation for the haemorrhages, and there is certainly no need to postulate either that the deposits are the late result of haemorrhage occurring in an active rheumatic process (Pendergrass and Leopold, 1945) or that they arise in that much debated lesion, acute rheumatic pneumonia.

The persistence of the nodules. The remarkable constancy of the radiological picture suggests a peculiarly slow removal of the deposits, but the possibility must also be considered of continually recurrent small haemorrhages. Experience of lobar pneumonia is apt to lead observers to believe that phagocytic scavenging in the pulmonary alveoli, as distinct from phagocytosis itself, is always extremely rapid, and particularly so if the substance to be removed is biologically inert; but in fact some of the 'inert dusts', as Gardner calls them, may be but slowly removed from pulmonary tissue. 'Frequently such overloaded phagocytes are found within the alveoli years after exposure to dust has ceased' (Gardner, 1940). The question arises whether iron is as inert as has been believed in the past. Certainly inorganic iron in the form of rouge (Fe_2O_3)

would appear to be virtually inert in the human lung; McLaughlin, Grout, Barrie, and Harding (1945) found in the lung of a silver finisher large deposits of this substance without any definite fibrosis of the lung, despite forty years in the trade, and Harding (1945) and Barrie and Harding (1947) found further similar cases at necropsy, again without fibrosis. Harding reviewed various earlier reports all pointing to the inert nature of iron oxide, although in a later paper (1948) he described a fine focal fibrosis in one such case. Few of these authors seem to have had a particular interest in the speed of removal of the foreign material from the lung, but one of Harding's rats (1945) injected tracheally with 0·5 to 1 ml. of a 5 per cent. suspension of rouge in saline showed an appreciable amount of rouge in the lung eight months later. Similarly McCord, Harrold, and Meek (1941), although they wrote that 'complete elimination of gross iron pigment from welding fumes from the lungs of laboratory animals appears to be a reasonable expectancy', found some iron deposit in the lungs of rats and rabbits nearly a year after exposure. More recently Doig and McLaughlin (1948) showed that the siderosis of welders is not necessarily permanent, and that after some years the radiological shadows may disappear. In contrast with this, the case of mitral stenosis described by Pendergrass, Lame, and Ostrum (1949), which was almost certainly one of haemosiderosis, showed nodulation in the skiagrams which scarcely altered over a period of 12 years.

Our study of the histology of the lung can scarcely tell us how long the nodules have been present, but it does provide some information about the happenings in the lung. It is quite certain, for example, that there must be repeated haemorrhage, because the first case could scarcely have survived if the haemorrhages corresponding to the haemosiderin deposits had all occurred at once. The fact that actual haemorrhages have so rarely been seen is no doubt due to the pre-terminal fall of pulmonary blood-pressure, and to the known rapidity of the phagocytosis of erythrocytes in the pulmonary alveoli (Strassmann, 1944). That the removal of haemosiderin from the alveoli is hindered can be reasonably assumed, since there is little evidence of iron in the peribronchial lymphatics or hilar nodes—a fact which is adequately explained by the fibroblastic reation in the stroma adjoining the filled alveoli. Haemosiderin is not an 'inert dust'. In the long-standing cases, as judged by the greater number of foci and by the greater structural abnormality around the affected alveoli, the alveoli are more tightly stuffed with siderophores than in the lesser cases; the 'queue' of phagocytes filling these alveoli indicates that fibrosis has blocked the channel of escape. If sufficient haemosiderin be present in a system of cognate alveoli, the iron released from this depot leads to damage and reaction in the adjacent tissue, and so strangles the lymphatic route of withdrawal.

Ceelen's Haemosiderosis

In 1931 Ceelen described a condition, occurring in childhood, of repeated intrapulmonary haemorrhage, with consequent gross deposit of iron in the lung, in some children accompanied by severe anaemia. A skiagram from one such patient (Professor Cappell's case) is given in our previous paper (Scott, Park,

and Lendrum, 1947). Since then, Wyllie, Sheldon, Bodian, and Barlow (1948) have described seven new cases and summarized the publications since 1931. To these may be added the recent reports of Barlow (1946), Waldenström (1948), Nancekievill (1949), and King (1949). The case mentioned by Engel and Newns (1939, foot of p. 390) may well be an example of Ceelen's haemosiderosis, and the earlier cases reported by Kockel (1899) and Sylla (1928) even though neither patient died in childhood, are probably further examples of this strange disease. The histological changes described by Wyllie, Sheldon, Bodian, and Barlow are identical with those which we have observed and attributed to the damaging effect of a locally high concentration of iron. The only difference is that in the cardiac cases the source of irritant iron is a focal accumulation of haemosiderin, and thus the damage is focal, whereas in Ceelen's haemosiderosis the haemorrhage, and therefore the damage, is widespread through the lung.

Diagnosis

For the radiologist the problem is to decide whether the pulmonary shadows are to be related to the cardiac lesion or to one of the many other causes of skiagraphic granularity. There is, of course, a natural reluctance to suggest tuberculosis in the patient with mitral stenosis, but two of our patients showed evidence of localized pulmonary tuberculosis of low intensity, and three examples of chronic fibroid tuberculosis were mentioned by Stone and Feil (1934) in a series of 100 cases of mitral stenosis. Both Rosenhagen (1928) and Preuschoff (1931) reported patients with mitral stenosis and nodular skiagrams who were found *post mortem* to have miliary tuberculosis of the lungs.

A composite list of the other causes of a spotted, granular, or marbled skiagram is given in our previous publication (Scott, Park, and Lendrum, 1947). To this may be added the recently described pneumokoniosis due to talc (McLaughlin, Rogers, and Dunham, 1949) and that due to graphite (Harding and Oliver, 1949; Gloyne, Marshall, and Hoyle, 1949; Doig, with a review of dust diseases, 1949). The coexistence of haemosiderosis and silicosis has recently been reported by Meiklejohn (1949). We are not prepared to deny the existence of a miliary hypostatic congestion, but suspect that the radiological appearances which have been so described in the past are usually due to haemosiderosis; and haemosiderosis apparently occurs in every case of mitral stenosis with right ventricular hypertrophy. Although it may rarely be enough to produce skiagraphic shadows its frequency, as proved microscopically, establishes its importance in differential diagnosis.

Focal Exudation in the Lung due to Cardiac Disturbance

Confining our attention to the exudates which are associated with cardiac upset, and leaving aside purpuric states, infections, poisonous gases, and embolic phenomena, we find two main forms, which may be described as the haemosiderotic and the fibrinous. Their obvious histological difference is matched by the very different degree of cardiac disability which produces them; the site in which they occur is the same.

The haemosiderosis of focal type which we have found in all our cases of mitral stenosis with right ventricular hypertrophy is without doubt related to the long-standing pulmonary hypertension, which in this disease can exist for many years with few or no symptoms. It is during this stage in the clinical course that we envisage rupture of the broncho-pulmonary anastomoses and the occurrence of repeated haemorrhages, each contributing more haemosiderin. It is to be noted that these haemorrhages are rarely gross enough to give rise to haemoptysis. Most of our patients had no haemoptysis in spite of the considerable quantities of haemosiderin present in the lung. It is perhaps significant that a few of our patients with mitral stenosis had an obvious iron-deficiency anaemia which could not be explained by external bleeding, infective endocarditis, or physiological loss of iron. We consider that enough iron can be lost into the alveoli to produce a moderate anaemia, just as in Ceelen's haemosiderosis there is sometimes severe anaemia.

Although, as has been stated, focal haemosiderosis is the typical result of mitral stenosis with right ventricular hypertrophy, it may also be seen in patients with systemic hypertension who survive several periods of left ventricular failure. In one patient, a woman of 41 years with long-standing low-grade pyelonephritis and severe hypertension, whose life had been maintained for months beyond clinical expectation, the lungs showed haemosiderosis greater in amount than in several of the mitral cases. We presume that in this, and in three other similar cases, each period of sublethal failure of the left ventricle was accompanied by a fall of systemic and therefore of bronchial arterial pressure. Since a fall of pressure in the pulmonary arteries in these circumstances is much less or even absent, there is a relative increase in the pulmonary arterial pressure. Thus there is produced intermittently, in the anastomotic plexus, a state of affairs closely similar to the more permanent dilatation believed to exist in patients with mitral stenosis. This observation of an apparently identical focal haemosiderosis in mitral stenosis and systemic hypertension may be correlated with the findings of Wood and Miller (1938). They found by injection methods that in every case of chronic rheumatic carditis there occurred 'a constant widening of the capillary anastomoses between the bronchial arteries and the branches of the pulmonary arteries' if there was 'hypertrophy of the right ventricle and failure of the right heart. Similar anastomoses occurred in cases of syphilitic heart disease, hypertension, and generalized arteriosclerosis, but were less constant and usually of milder degree than in cases of rheumatic heart disease.' The occurrence of focal haemosiderosis in these hypertensive cases obviously supports our view that the haemorrhages in patients with mitral stenosis are of mechanical causation.

The other type of pulmonary exudate, the fibrinous, is characteristically found in diseases giving rise to acute pulmonary oedema from failure of the left ventricle. In these cases the morbid anatomist is generally dealing with a disturbance of haemodynamics which has progressed fairly rapidly to a fatal issue, and the histological picture therefore shows no extended development, and moreover is complicated by the further disturbances of the agonal period. In

addition to the fibrinous deposits to be described below, and to haemorrhages and oedema, both of which may be in part agonal, deposits of haemosiderin are present in some of these lungs, and are evidence of previous left ventricular failure. An example of the pulmonary changes due to a severe but brief attack of cardiac asthma uncomplicated by terminal cardiac failure was seen in a pregnant hypertensive woman, who died from an obstetric mishap three weeks after she had apparently regained her cardiac efficiency. In her lungs there were a few small characteristic deposits of haemosiderin, but in addition there were fibrinous coagula situated in groups of adjacent alveoli (Plate 20, Fig. 10).

The results of severe left ventricular failure rapidly progressing to death have been observed in cases of established hypertension, both essential and nephritic, of glomerulonephritis of short duration and high intensity, and of active rheumatic myocarditis, both primary and recurrent. In all these examples of left ventricular failure the obvious histological finding is a digitate mass of fibrin situated in the alveolar duct and projecting into the alveoli; occasionally this condition is widespread (Plate 20, Fig. 11), but more commonly it has to be looked for. The coagula are easily missed with the ordinary staining methods, especially when, as frequently happens, there is haemorrhage as well as fibrin, but the use of the picro-Mallory stain (Lendrum, 1949), with its red fibrin contrasting with yellow blood, allows immediate recognition of the fibrin and easy appreciation of its distribution. The fibrinous deposits show certain variations in form which may be fortuitous rather than indicative of a different origin. The characteristic form is virtually a cast of the alveolar duct with its related alveoli (Plate 20, Figs. 11 and 12), and is apparently identical with the exudate described by Doniach (1947) in his study of the lung in so-called uraemic oedema. One variant shows a central air core, as if the air column had pushed the forming exudate outwards, forcing it against the wall of the alveolar duct so that a membrane is formed across the alveolar mouths, continuous with the underlying tangle of fibrin in the alveoli. This has been seen as a scattered phenomenon (Plate 21, Fig. 13) in rheumatic and nephritic cases, and as a generalized phenomenon in rheumatic cases (Plate 21, Fig. 14), but we have not seen this air-excavated exudate in instances of left ventricular failure following established hypertension. A similar histological appearance due to the pressure of the air column is often seen in the lungs with haemosiderosis, the siderophores being forced down and out of the duct into the alveoli (Plate 21, Fig. 15). A variant of the membranous form of alveolar-duct exudate is an apparent coagulum, again plastered over the wall of the alveolar duct; this membrane is not fibrin, either structurally or tinctorially (Plate 22, Fig. 16). It recalls the appearances seen in so-called vernix pneumonia, and we have found it so far only in cases with rheumatic myocarditis. In all these forms of exudation there is a sharp localization of the exudate to the alveolar duct and its related alveoli, and from this we conclude that the haemodynamic strain due to a rapid loss of balance between the power of the two ventricles is made manifest at the weakest link, which is the broncho-pulmonary anastomosis.

In three of the 26 cases of mitral stenosis and haemosiderosis an osseous mass

was found (Plate 22, Fig. 17), of the focal type known to occur in patients with mitral stenosis (Elkeles and Glynn, 1946, with references; Lawson, 1949). The disposition of the bone resembles that of the fibrinous casts described above, and suggests that it originates in them. These osseous masses have not been frequently reported but, as Hamilton observed (1894), fibrinous deposits are rare in patients with mitral stenosis; they are common only in association with a cardiac lesion so grave that recovery is unlikely and prolonged survival improbable. Against this theory of their origin is the fact that in two of our cases the ossified masses are larger, and occupy apparently more alveoli, than any of the fibrinous deposits we have observed, but it must be remembered that the manoeuvres of fixation, dehydration, and embedding produce considerable shrinkage of tissues other than bone. The shape of the ossified mass and its relation to the alveolar walls points to its origin in a deposit situated in the air-space of the lung, a deposit which has somehow escaped ordinary fibrotic organization.

If, as seems probable, there is a broncho-pulmonary capillary anastomosis in the terminal bronchioles, the pressure gradient presumably falls from the bronchial artery side to the pulmonary artery side of the plexus. A rise in pulmonary vascular pressure gradually occurs when mitral stenosis is accompanied by right ventricular hypertrophy, and will resist the flow across the anastomotic plexus. We believe that when, on the other hand, the systemic pressure in the bronchial artery falls owing to left ventricular failure, acute stasis develops in the plexus, and that this, if uncomplicated by thrombosis, is the origin of the fibrinous exudate. A confirmation of this hypothesis is implied in the case of a girl of 18 years with stenosis of the mitral and tricuspid valves, who had been admitted to hospital for the tenth time with arthralgia and pericarditis. Histological examination of the lung stained by the acid picro-Mallory method (Lendrum, 1949) shows the alveolar capillaries distended with normal (yellow-stained) erythrocytes, but the capillaries of the terminal respiratory bronchioles and of the proximal part of the alveolar ducts are all occluded and distended by a red-staining core of fibrin (Plate 22, Fig. 18). The sharp localization of fibrin to these capillaries is much too widespread to be due to embolism, and implies that these vessels are off the line of the main blood-stream and have been the site of a peculiarly severe stasis. We believe that these vessels are in fact the anastomotic plexus, and that the intravascular thrombosis shows the plexus to extend from the respiratory bronchiole distally to the wall of the alveolar duct. The myocardial changes in the left ventricle and the pericarditis are adequate to explain a fall of pressure in the bronchial artery, with consequent stasis in the anastomotic plexus. In considering all the forms of exudate described in this section it is difficult to escape the conclusions that all come from the broncho-pulmonary anastomoses, that they have a mechanical basis, and that the differences in their histological character merely reflect the speed of their formation, modified in part by the pre-existing state of the pulmonary circulation.

We owe a debt of thanks to many friends for material, for clinical data, and for helpful discussion, particularly to Dr. George Allan, Professor Cappell, and Professor McNee of Glasgow, Dr. J. Gordon Clark, Dr. J. M. Morgan, and Professor Patrick of Dundee, Professor Gough of Cardiff, and Dr. Walter Pagel and Professor Russ of London. We are also especially grateful to those who by their technical skill have played so important a part in our studies, Messrs. W. Carson and W. Penny of Glasgow, and Messrs. J. W. Corkhill and D. S. Fraser of Dundee.

Summary

In the lungs of patients who have mitral stenosis accompanied by hypertrophy of the right ventricle there are focal accumulations of haemosiderin. In some instances these show in the skiagram, giving the picture which in the past has been called miliary congestion. This focal haemosiderosis does not occur in the absence of right ventricular hypertrophy: for example, when tricuspid stenosis is also present.

The haemosiderin is situated in groups of adjacent alveoli, and its distribution points to the wall of the terminal bronchiole, where the capillary anastomoses between bronchial and pulmonary arteries are believed to lie, as being the site of haemorrhage. These haemorrhages are probably of mechanical origin, frequently repeated, and usually unaccompanied by haemoptysis. Around the deposits of haemosiderin there is ferrous impregnation of elastica and reticulin, with breakdown of these structures; the resulting fibrosis obstructs the lymphatic withdrawal, and so perpetuates and intensifies the dangerous concentration, of intra-alveolar haemosiderin. The pulmonary damage seen in Ceelen's haemosiderosis is of identical type, but generalized, whereas the condition here described is characterized by the striking normality of the pulmonary tissue between the deposits.

The morbid anatomy of pulmonary exudations occurring in other forms of cardiac upset suggests that haemosiderosis is the mark of a long-standing right ventricular preponderance. This is generally due to mitral stenosis, but an identical picture is produced in cases of systemic hypertension if left ventricular failure has been prolonged or repeated. When a more rapidly fatal left ventricular failure occurs, as in cases of hypertension, glomerulonephritis of short duration, or rheumatic carditis, the pulmonary exudate is seen as a fibrinous cast of the alveolar duct and its related alveoli. The osseous mass seen in three of our cases of mitral stenosis is possibly the late result of such a fibrin cast. It is believed that the situation of these fibrinous casts again points to an origin from the anastomotic vessels of the terminal bronchioles, and that these casts, like the haemosiderin foci, are the result of loss of balance between the ventricles, the alteration of relative pressure in the pulmonary artery and bronchial artery having led to exudation from the anastomotic plexus. In some cases of severe rheumatic carditis solid fibrinous plugging was found, not only of the vessels lining the terminal bronchioles, but also of the vessels of the alveolar duct wall. This observation suggests that the anastomotic plexus spreads farther down than had previously been suspected.

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FIG. 2. Haemosiderosis. X-ray of the chest of a man aged 38, with mitral stenosis and miliary shadows in the lung which remained essentially unchanged for eight months

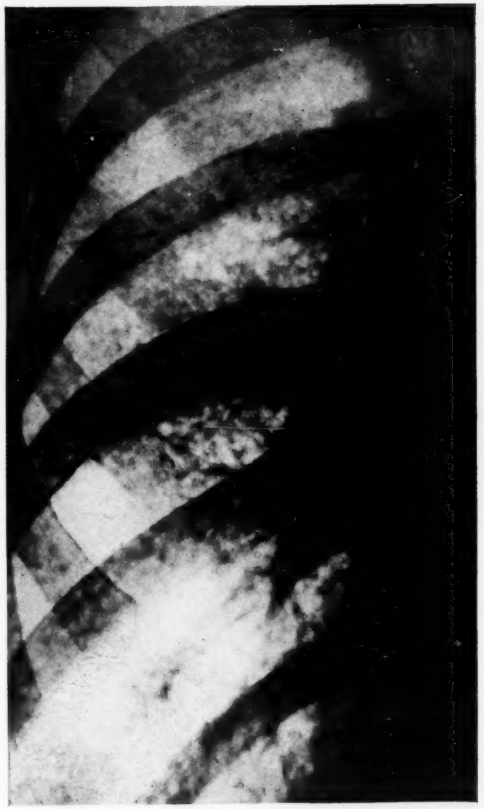

FIG. 3. Enlargement of a section of Fig. 2

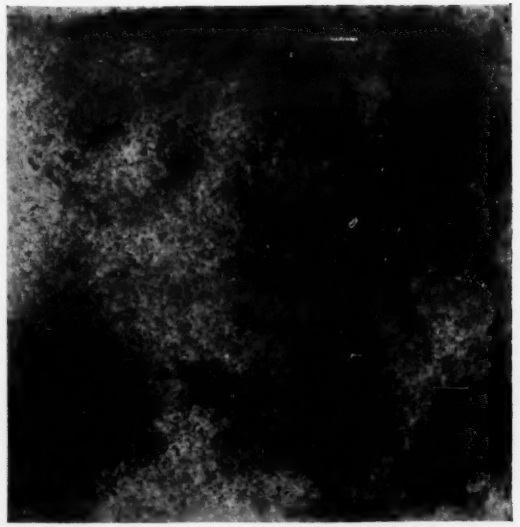

FIG. 4. X-ray of a random dispersion of extremely fine iron filings in wax

FIGS. 2, 3, and 4 are reproduced by courtesy of the *British Journal of Radiology*

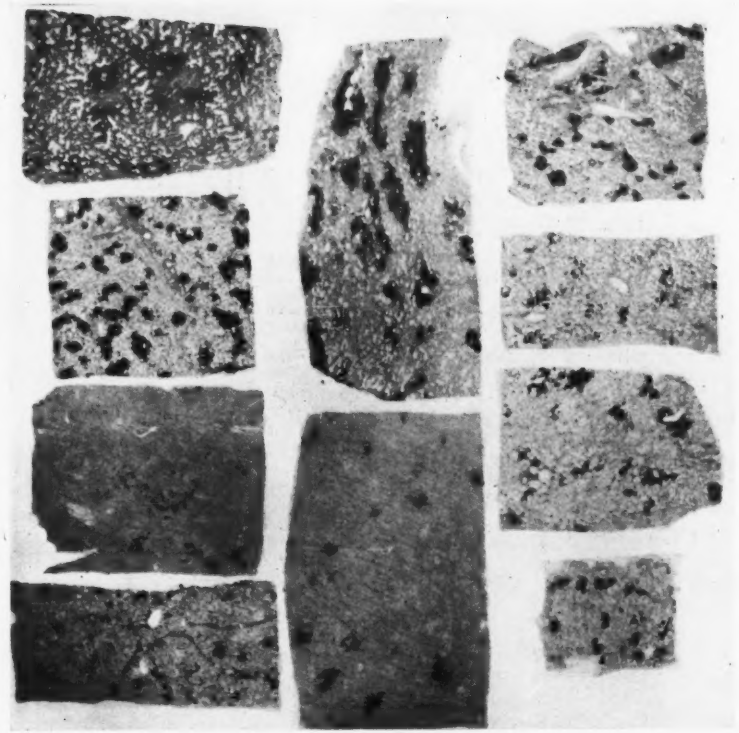

FIG. 5. Sections of lung from 10 cases of haemosiderosis associated with mitral stenosis (Perls method, $\times 1{\cdot}7$)

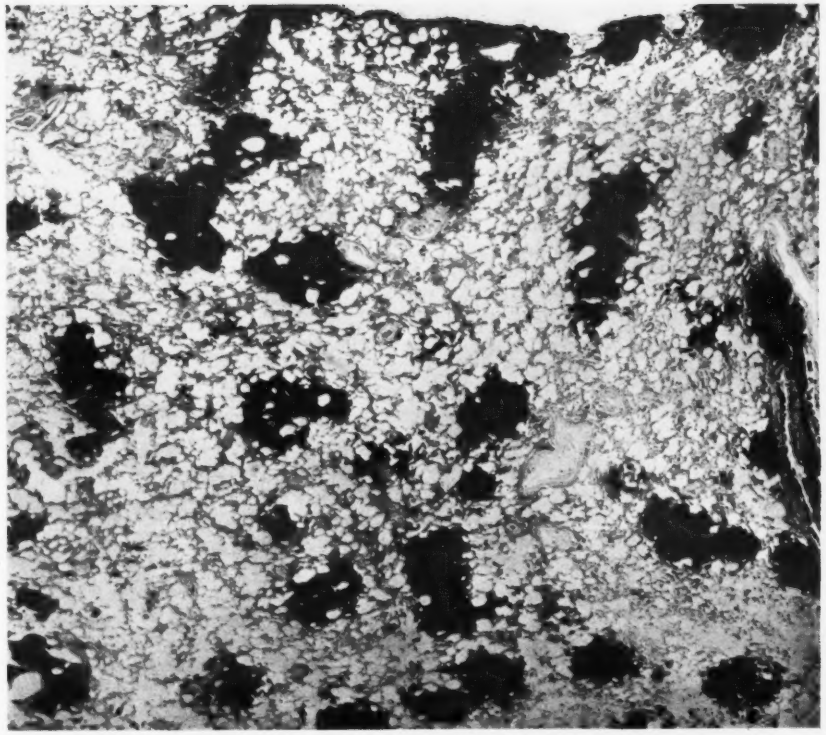

FIG. 6. Lung, showing the haphazard distribution of nodules, and normal intervening alveolar tissue (Perls method, $\times 7\frac{1}{2}$)

FIG. 7. Each nodule (Fig. 6) is seen to consist of a group of adjacent alveoli. Their lumens are filled with material (black), and their walls show fibrous thickening, but the intervening lung is normal (picro-Mallory, $\times 13\frac{1}{2}$)

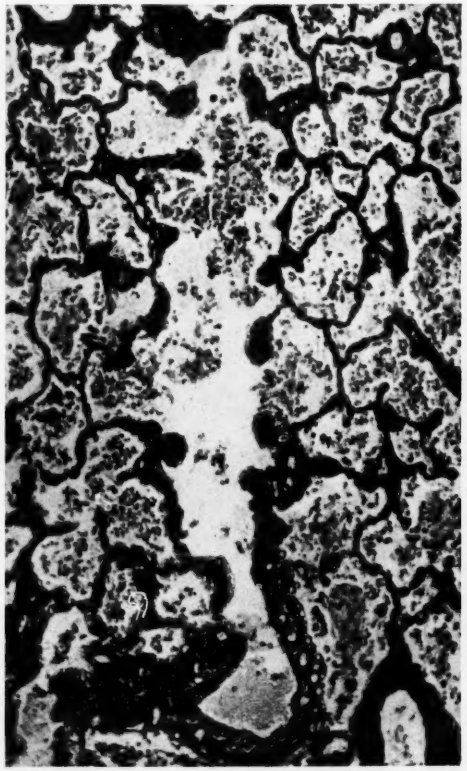

FIG. 8. Alveolar duct cut longitudinally. The musculo-elastic wall at the alveolar mouths appears as club-shaped knobs, with an enlargement characteristic of mitral stenosis. The hypertrophy affects muscular, elastic, and collagenous tissues (picro-Mallory, $\times 64$. Orange filter)

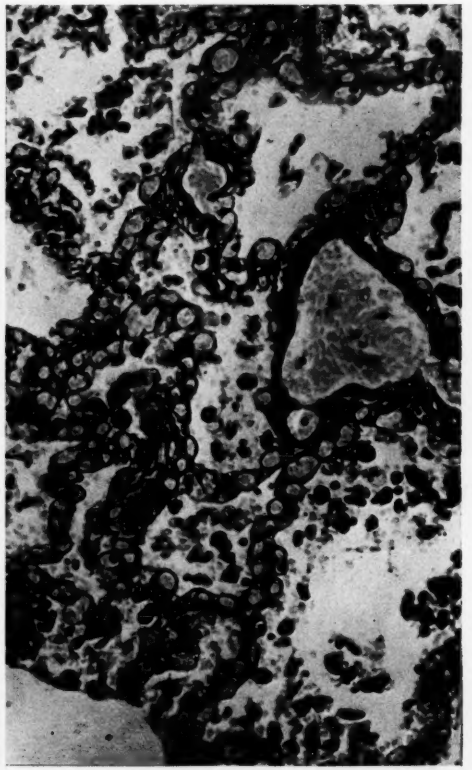

FIG. 9. Lung from one of the few cases with varicosity of the alveolar capillaries. The free way in which they bulge is against the view that there is a fibrous thickening of their walls (carbacid-fuchsin, $\times 255$)

FIG. 10. Coagulum of fibrin lying in a group of alveoli, from a patient with essential hypertension who had experienced a brief partial failure of the left ventricle some three weeks before her death from an obstetric mishap. Note the minimal amount of organization present after three weeks, and the normality of the surrounding lung (picro-Mallory, $\times 83$)

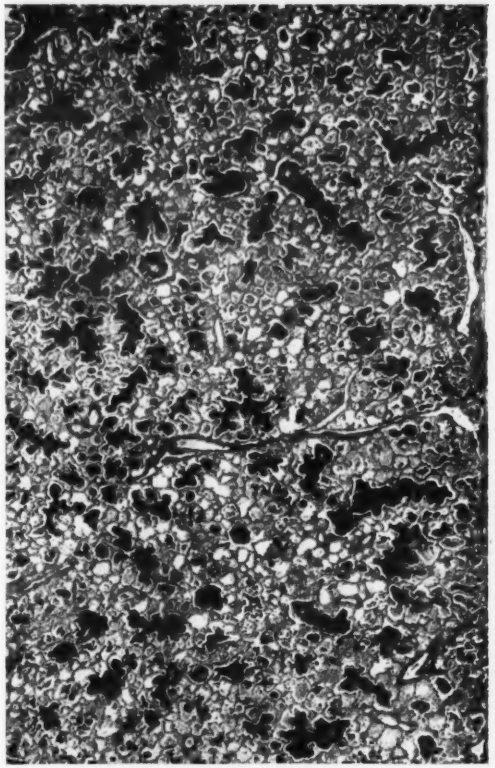

FIG. 11. Fibrin casts in the alveolar ducts over a wide area of lung, with no suggestion of pyogenic inflammation. The patient was a girl of 14 years, with rheumatic heart disease for one year terminating in active rheumatic myocarditis (picro-Mallory, $\times 15$, minus-red filter)

FIG. 12. Duct and its alveoli filled with a fibrin cast, in an area of widespread haemorrhage, from a case of nephritis of seven weeks' duration (picro-Mallory, $\times 215$. By this method erythrocytes are yellow and fibrin red. Photographed with minus-red light)

FIG. 13. Fibrin cast from the lung of a pregnant woman aged 24 who died of rheumatic pancarditis, showing 'membrane' formation. The air in the duct has pushed into the fibrin from above and stretched it across the alveolar mouths. During dehydration, &c., the fibrin shrinks more than the surrounding tissues (phosphotungstic haematoxylin, ×125)

FIG. 14. Alveolar ducts outlined by a fibrinous membrane from a young child with active rheumatic pancarditis. The distended ducts contrast with the rather collapsed alveoli. This exact appearance is rarely seen in conditions other than rheumatic pancarditis (phosphotungstic haematoxylin, ×67)

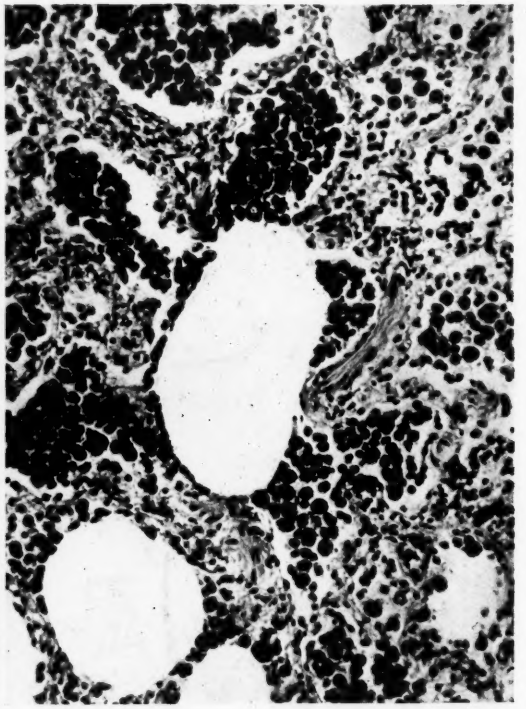

FIG. 15. Haemosiderosis focus cut through the alveolar duct. The air column has pushed the siderophores (as it has the fibrin in Figs. 13 and 14) outwards and into the alveoli. Part of the spiral musculo-elastic is seen on the right of the duct, enlarged as it usually is in cases of mitral stenosis (haematoxylin and eosin, ×175)

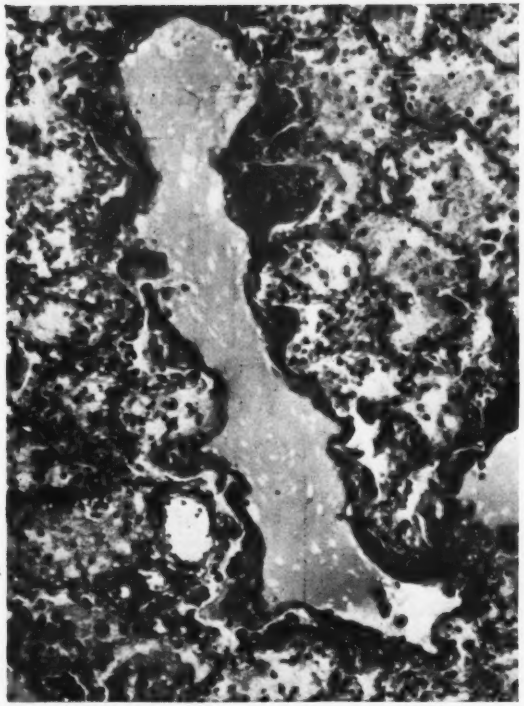

FIG. 16. Alveolar duct from a case of active rheumatic carditis. It is lined by a membrane, non-fibrinous except at one spot at the upper end. It is of interest that the duct contains fluid, whereas the occluded alveoli contain air (picro-Mallory, ×140)

FIG. 17. Ossified mass from a case of mitral stenosis with haemosiderosis. The bone in this, as in the other two examples referred to in the text, is intra-alveolar. The ring of apparent emphysema may possibly be artefact (celestin blue, haemalum and light green, ×38)

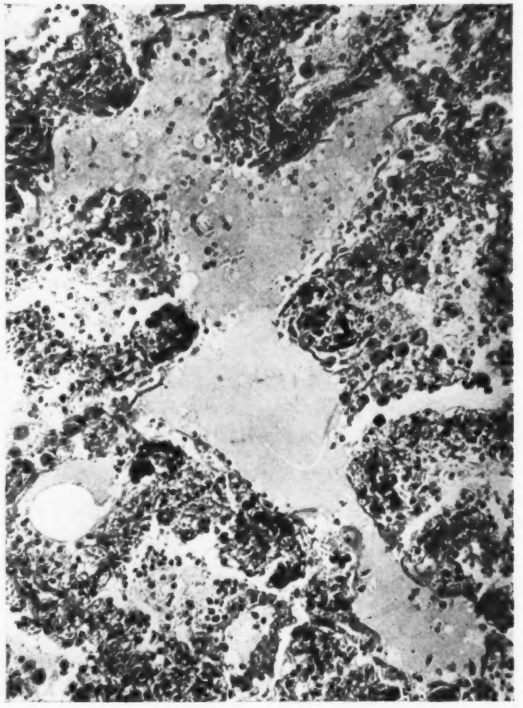

FIG. 18. Alveolar duct containing oedema fluid, from the case of rheumatic disease described on page 260. In all the portions of lung examined from this case, the capillaries lining the respiratory bronchioles and alveolar ducts were plugged with a firm core of fibrin, black in the figure (picro-Mallory, ×160)

616.36–074

A CRITICAL REVIEW OF CHANGES IN LIVER FUNCTION DURING LIVER DISEASE[1]

By CHARLES H. GRAY

(From the Department of Chemical Pathology, King's College Hospital, London)

Tests of Liver Function

The most commonly employed tests of liver function may be usefully classified in three groups.

1. Tests of excretory function: (*a*) Serum-bilirubin estimation and the van den Bergh reaction; (*b*) urinary bile-pigment tests; (*c*) dye tests.

2. Tests of metabolic function, including (*a*) glycogen formation; (*b*) protein metabolism and synthesis; (*c*) fat metabolism; (*d*) conjugation.

3. Empirical tests.

1. *Tests of excretory function*

(*a*) *Serum-bilirubin and the van den Bergh reaction.* The determination of serum-bilirubin by some modification of the van den Bergh reaction, such as that of Malloy and Evelyn (1937) or that of Haslewood and King (1937), may indicate whether or not there is failure of the excretory function of the liver. This failure may be merely relative to a greatly increased haemolysis of red cells and the need for increased excretion of bilirubin, as in haemolytic jaundice or anaemia, or absolute, as in hepatogenous and obstructive jaundice. In haemolytic jaundice the direct van den Bergh reaction is usually, but not always, negative, while in hepatogenous and obstructive jaundice the direct van den Bergh reaction is always positive (C. H. Gray, 1947).

(*b*) *Urinary bile pigments.* Failure in the excretory function of the liver demands the excretion of bile pigments by the kidney and, as will be seen later, it is of considerable importance to investigate the *urine*, not only for the presence of bilirubin, but also for the presence of urobilinogen and urobilin, by Ehrlich's aldehyde test and Schlesinger's zinc fluorescence test respectively. The bile-pigments are normally reduced in the gut to stercobilinogen, which is re-absorbed into the blood-stream and re-excreted into the bile by the liver. The diseased liver is unable to re-excrete this stercobilinogen, which is therefore eliminated by the kidney and causes the urobilinogen and urobilin reactions in the urine to become positive. It is now generally agreed that tests for bile-salts in the urine are unsatisfactory and of limited value, owing to the fact that the liver plays a part both in the manufacture and in the disposal of bile-salts (Bollman and Mann, 1936).

(*c*) *Dye tests.* In America the excretory function of the liver has been investigated in patients without jaundice by measuring the ability of the liver to remove

[1] Received March 4, 1950.

certain substances such as brom-sulphthalein (Magath, 1936) and bilirubin (Soffer and Paulson, 1934) from the blood-stream. Such investigations have not been widely practised in this country because the necessary materials are not in ready supply.

2. *Tests of metabolic function*

(*a*) *Glycogen formation.* Two methods have been used to measure glycogenic function: they are the laevulose and galactose tolerance tests. The original form of laevulose tolerance test, in which the total reducing substances in the blood, including glucose and laevulose, were determined after oral administration of laevulose, has been superseded by a modification of the test in which the concentration of laevulose in the blood is specifically measured (Herbert and Davison, 1938). Laevulose tolerance is abnormal at certain stages of liver disease, as will be shown later, but its value as a test of hepatic function is vitiated because there is evidence that laevulose is partly utilized by extra-hepatic tissues (Bollman and Mann, 1931). Galactose is said to be converted by the liver to glycogen with much less utilization outside the liver (Bollman, Mann, and Power, 1935), and is therefore preferable to laevulose for the investigation of glycogenic function (Maclagan, 1940). The rate of absorption of galactose from the gut appears to be affected by extra-hepatic factors such as hyperthyroidism (Barnes and King, 1943) and theoretically it appears to be better to administer it intravenously. When this is done, the level of blood-galactose immediately after the test-dose varies considerably from case to case (King and Aitken, 1940), and interpretation of the results is difficult. There is therefore probably little to choose, as a measure of glycogenic function, between the oral laevulose tolerance test in its modern form and either the oral or the intravenous galactose tolerance test.

(*b*) *Protein metabolism and synthesis.* (i) *Urinary and plasma amino-acids.* It has long been known that in acute necrosis of the liver there is a reduction of the de-amination of amino-acids, with the result that the blood-urea is diminished, while there is an increase of the plasma amino-acid concentration, and with it of the urinary amino-acids. This may result in crystallization of the less soluble amino-acids leucine and tyrosine in the urine, but only in very severe damage to the liver. It is probable that the recent development of filter-paper partition chromatography (Dent, 1946), whereby the amino-acids in 0·05 ml. of urine may be easily identified and their level roughly assessed, may enable us to recognize failure of de-amination in less severe degrees of liver failure. This technique will no doubt be much more widely used in the near future, and will provide a useful tool in the investigation of liver function, because it is much simpler than the complicated analysis of plasma amino-acids.

(ii) *Protein synthesis.* It is now well recognized that plasma-albumin and plasma-prothrombin (Hoagland and Shank, 1946; Lord and Andrus, 1941) are diminished in severe liver damage, presumably owing to an impairment of synthesis. In long-standing liver disease malnutrition may also be of importance. The lowered plasma-albumin level may be a factor in the production of oedema.

Hypoprothrombinaemia due to liver damage may be readily distinguished from hypoprothrombinaemia due to obstructive jaundice (Stein, 1944). In liver disease the prothrombin time as measured by the method of Quick, Stanley-Brown, and Bancroft (1935) remains prolonged despite adequate parenteral administration of vitamin K, whereas in obstructive jaundice it rapidly returns to normal with parenteral vitamin K therapy. At certain stages of liver disease there is a qualitative alteration in the serum-proteins. Electrophoresis shows that this usually consists of an increase in the γ-globulin fraction (Martin, 1946, 1949 *a*). Such special studies are not usually available in hospital practice, but sometimes the alteration is enough to give a significant increase in the total amount of globulin measured by the more common methods, such as precipitation with 22 per cent. sodium sulphate followed by micro-Kjeldahl distillation (Harrison, 1947). However, when the qualitative partition of the serum-globulins becomes abnormal in liver disease, certain empirical precipitation and flocculation reactions often become positive. These include the Takata-Ara reaction (Jezler, 1930) with mercuric chloride, the cephalin-cholesterol flocculation test (Hanger, 1939) with a specially matured preparation of cephalin, the colloidal gold (S. J. Gray, 1940) and Scharlach-red (Maizels, 1946) tests, the thymol turbidity test (Maclagan, 1944 *a*), and the zinc sulphate test (Kunkel, 1947). Of these there is little doubt that the thymol turbidity and zinc sulphate tests are the most useful, since the reagents are much more readily prepared under standardized conditions. The Takata-Ara reagent is equally readily prepared, but unduly sensitive in that it gives too many positive results in obstructive jaundice (Shulman, Steigmann, Popper, and Stevens, 1949). These tests must all be of much the same fundamental significance. Some may be more sensitive than others, and their difference in sensitivity must depend on minor differences in the nature and amount of the various plasma-proteins. Thus Martin (1949 *b*) has shown that the strong thymol turbidity reaction given by γ-globulin can be reduced progressively to nil by the addition of increasing amounts of albumin. These tests are believed to indicate not liver damage as such, but a specific response of the serum-proteins to liver damage. In some cases of fatal acute necrosis this response fails to occur, and the reactions remain negative. Attempts have been made to interpret the results of the various liver function tests by relating them to the specific response of various body-proteins (Popper, Steigmann, de la Huerga, and Franklin, 1949).

(*c*) *Fat metabolism.* There is no easy method of assessing one important function of the liver—its ability to manufacture ketone bodies. The only clinical test of liver function in relation to fat metabolism is the determination of the proportions of free and ester cholesterol in the blood-plasma, but the technique is much too time-consuming and difficult for routine use. Cholesterol is excreted by the liver, and therefore increased total cholesterol is found in the blood in both hepatogenous and obstructive jaundice. Sherlock (1946 *b*) showed that determination of the blood-cholesterol is of little use in the diagnosis of obstructive jaundice from acute hepatitis and cirrhosis with jaundice.

(*d*) *Conjugation of certain substances.* In estimating this function the ideal

procedure would be to assess the conjugation by the liver of endogenously produced substances such as steroid hormones. Tests with steroid hormones are impracticable with our present knowledge and, as is well known, the most commonly employed method of estimating the efficiency of the liver in conjugation is the hippuric acid synthesis test in which hippuric acid secretion is measured after the administration of sodium benzoate. Such estimations must always be accompanied by a test of renal function (Sherlock, 1946 *a*), since even if conjugation by the liver were proceeding efficiently and rapidly, it would be masked if renal failure were present. In the earlier form of the test four gm. of sodium benzoate were given by mouth, and the urine was collected for a period of four hours (Quick, 1936); but since this method often provoked nausea, if not vomiting, absorption was an uncontrolled factor. The method now used is to administer 1·77 gm. of sodium benzoate intravenously, and to determine the urinary excretion of hippuric acid during the next hour (Quick, 1939). Sherlock (1946 *b*) showed that although hippuric acid synthesis is impaired in liver disease its impairment is not proportional to the damage estimated from biopsy of the liver, and is no greater when the degree of damage is severe than when it is less marked. The estimated synthesis seldom falls below 45 per cent. of normal, possibly owing to hippuric acid synthesis by extrahepatic tissues; but a similar result would be given by the excretion of unchanged sodium benzoate by the kidney (Moser, Rosenak, and Hasterlik, 1942). The proportion of sodium benzoate excreted unchanged may depend on the rate of injection, and since unchanged benzoate would be estimated as hippurate by ordinary methods, its excretion would seriously limit the usefulness of the intravenous sodium benzoate test in assessing hepatic function.

3. *Empirical tests*

(*a*) *Serum alkaline phosphatase.* The liver secretes phosphatase into the bile. It is therefore not surprising that whereas in retention (haemolytic) jaundice the serum or plasma alkaline phosphatase is usually within normal limits, in regurgitation (hepatogenous and obstructive) jaundice it is above normal, presumably owing to the regurgitation of bile constituents into the bloodstream. It is not clear why a very high percentage of cases of obstructive jaundice show serum-phosphatase concentrations above 35 units per 100 ml., while a very high percentage of cases of hepatogenous jaundice show a serum-phosphatase between 13 and 35 units per 100 ml. (Maclagan, 1944 *b*). Nevertheless the determination of serum or plasma alkaline phosphatase provides a useful, though not a diagnostic, empirical test of hepatic function.

(*b*) *Urinary coproporphyrin.* Several workers (Nesbitt and Snell, 1942) have proposed the quantitative measurement of urinary coproporphyrin excretion as an index of hepatic function. The present author can confirm the view that in acute hepatitis the urinary excretion of coproporphyrin is above normal in many cases, but not in all. It has not been possible to correlate this variability with the various stages of the disease. The method recently published by Schwartz, Hawkinson, Cohen, and Watson (1947) for specific estimation

of the I and III isomers may be of value, especially perhaps in chronic hepatitis.

Changes in Liver Function during Liver Disease

The ultimate value of a liver function test depends on the percentage of positive results found in a large number of investigations of patients with liver disease. The higher that percentage, the more effective is the test considered to be, provided a low enough percentage is found in normal persons and in patients with diseases in which liver function is not disturbed. Surveys of the literature reveal that different laboratories obtain by this standard very different impressions of the value of a given test in acute hepatitis. The reason may be that insufficient attention has been paid to the stage of the disease at which each test is performed. It has been known for a long time that the appearance of urobilinoid substances in the urine is dependent on the severity and stage of liver disease. Ehrlich's and Schlesinger's tests become positive in the earliest stages of acute hepatitis, but if the jaundice is severe these tests become negative at the height of the disease, presumably owing to the absence of stercobilinogen in the gut. With recovery and the subsidence of jaundice the tests for these substances again become positive. As regards the glycogenic functions of the liver, laevulose tolerance may be diminished in acute hepatitis even before the appearance of jaundice, but in most cases the tolerance becomes normal within a very few days of the development of jaundice (C. H. Gray, 1945). Sherlock (1946 *b*) found that galactose tolerance returned to normal, on the average, within 14 days of the onset of the disease. She observed 'that the method is insensitive'; but there is an alternative explanation. Dible, McMichael, and Sherlock (1943) pointed out that hepatic damage in acute hepatitis may reach its maximum even before the appearance of jaundice. It is also known that while the regeneration of liver cells is ordinarily very rapid, restoration of the normal architecture of the liver takes a much longer time. In the early stages of acute hepatitis the zonal necrosis of the liver cells may be accompanied by their failure to perform their normal metabolic functions, such as the synthesis of glycogen from monosaccharides. The newly formed liver cells which rapidly make their appearance are fully able to carry out this function, and therefore the galactose and laevulose tolerance tests become negative long before restitution of the normal architecture of the liver permits biliary excretion to become normal.

Higgins, O'Brien, Stewart, and Witts (1944) also observed that liver function tests are not equally useful in the different stages of the disease. They showed that in acute hepatitis of more than eight weeks' duration the concentration of plasma-albumin may be diminished, while that of plasma-globulin may be increased. The change in albumin concentration may in many cases be due to malnutrition, but impaired synthesis may play a part in those cases in which progressive damage is leading to cirrhosis of the liver. The alteration in globulin concentration is probably related to the changes of protein-partition known to occur in liver disease. These give rise to the various flocculation and

precipitation reactions, which again may show changes during the course of acute hepatitis. An attempt to record the changing results of hepatic function tests during the different stages of the disease was made by Watson and Hoffbauer (1947), who published a diagram showing admirably the changes which occurred in certain function tests during a moderately severe attack of acute hepatitis. Their diagram failed to emphasize sufficiently the effect of differences in the severity and duration of the condition. Hoffbauer, Evans, and Watson (1946) proposed profiles of liver function tests in which the results of a considerable number of tests were plotted above and below a line representing the normal result. The graph-profiles are of different kinds according to the type of liver disease investigated. Not every worker approves of such a multiplicity of tests for the investigation of hepatic disease, and the main purpose of this review is therefore not to present any new tests or to describe any fundamental research, but to emphasize the way in which the results of the commoner liver function tests vary according to the stage, severity, and progress of the disease. This variation has important practical applications, since tests which are of great value at certain stages may be relatively useless at others.

Acute Hepatitis

Acute hepatitis is a disease of greatly varying severity and duration, and Fig. 1 represents what is generally accepted as the clinical course of acute hepatitis. The short pre-icteric stage of a few days may end in recovery without the development of overt jaundice or, rarely, may progress rapidly to acute hepatic necrosis and death before jaundice has time to develop. More frequently the pre-icteric is followed by the icteric phase, which varies greatly in its intensity and duration. On rare occasions acute necrosis may result in early death, but usually the icteric phase is followed within a short period by recovery. Often, however, it persists for 10 weeks or more, and while recovery after this time frequently occurs, it is not uncommon for these patients to pass through a subacute stage terminating in a chronic fibrosis which is indistinguishable from cirrhosis of the liver.

Pre-icteric stage. Neefe, Stokes, Reinhold, and Lukens (1944) and Pollock (1945 *a*) showed that during the pre-icteric phase there is bilirubinuria, as indicated by a positive Fouchet test. A van den Bergh test performed on the plasma shows that the direct reaction has become positive, although the concentration of bilirubin is not raised above normal. A little later, but still during the pre-icteric stage, urobilin and urobilinogen appear in the urine. Tests of glycogenic function, such as the laevulose tolerance test, show impairment in the few cases which have been studied at this stage. Pollock (1945 *b*) pointed out that the results of the hippuric acid synthesis test show progressive improvement from the time the patient is admitted to hospital. Most of his cases were investigated within three days of the appearance of jaundice, but one case, reported earlier (Pollock, 1945 *a*), was found to have impairment of hippuric acid synthesis during the pre-icteric stage, and this earlier impairment of func-

tion may be the general rule. The precipitation and flocculation tests do not become positive until a later stage in the disease, when we should expect regeneration of the liver cells to be well established.

Short icteric stage. If the pre-icteric stage clears up we have acute hepatitis without jaundice, but as far as is known jaundice and hyperbilirubinaemia more usually supervene, the direct van den Bergh reaction remaining positive. The quantities of bilirubin, urobilinogen, and urobilin in the urine increase

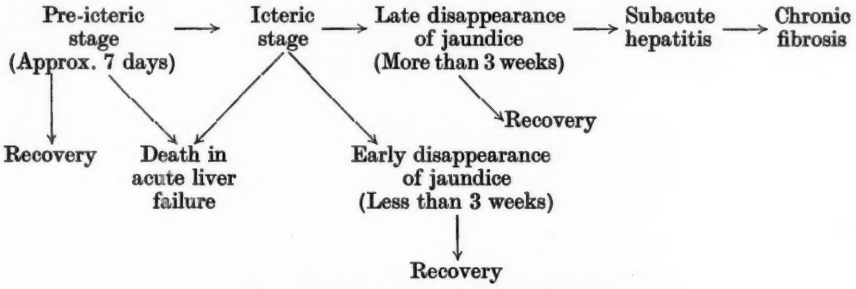

FIG. 1. Clinical course of acute hepatitis.

considerably, and the stools become clay-coloured. At this stage the tests of impaired glycogenic function, such as those of laevulose and galactose tolerance, may remain positive, but more usually they become negative within a day or two of the appearance of jaundice. This is almost always the case with patients whose jaundice is of short duration and not severe. The ability to synthesize hippuric acid appears to be impaired for a variable but somewhat longer period. Plasma-phosphatase appears to be increased at about the time when jaundice develops, or a little later, and a little later still the empirical flocculation tests become positive. In many cases the jaundice clears up rapidly, i.e. within two or three weeks of its development. Bilirubin usually disappears from the urine while hyperbilirubinaemia is still present, but urobilinogen and urobilin persist in the urine until jaundice has completely gone. Frequently the flocculation and precipitation reactions, as well as the plasma-phosphatase, remain abnormal for some time after the clinical evidence of jaundice has vanished, but eventually become normal if complete recovery occurs.

Long icteric stage. Not all cases of acute hepatitis run this short course; in some patients jaundice becomes intense and remains so for weeks. It will be convenient to consider separately those cases in which complete recovery ultimately occurs and those in which chronic fibrosis supervenes. There is usually intense jaundice, and little bile reaches the gut, so that urobilin and urobilinogen disappear from the urine. In patients who will eventually recover, the laevulose and galactose tolerance tests return to normal, in most cases within about 14 days, and otherwise a very little later. Usually flocculation tests are positive and plasma alkaline phosphatase is increased, but not to the levels observed in obstructive jaundice. Nevertheless the diagnosis between these two diseases may occasionally be difficult. An obstructive jaundice likely

to be confused clinically with this stage of acute hepatitis is most often due to malignant obstruction. Hippuric acid synthesis tests are of little value, but repeated determinations of faecal stercobilinogen by the method of Schwartz, Sborov, and Watson (1944) will reveal that in acute hepatitis significant traces of bile-pigment reach the gut. Where hepatitis lasts two months or more, serum-albumin tends to be low, and serum-globulin to be increased. When

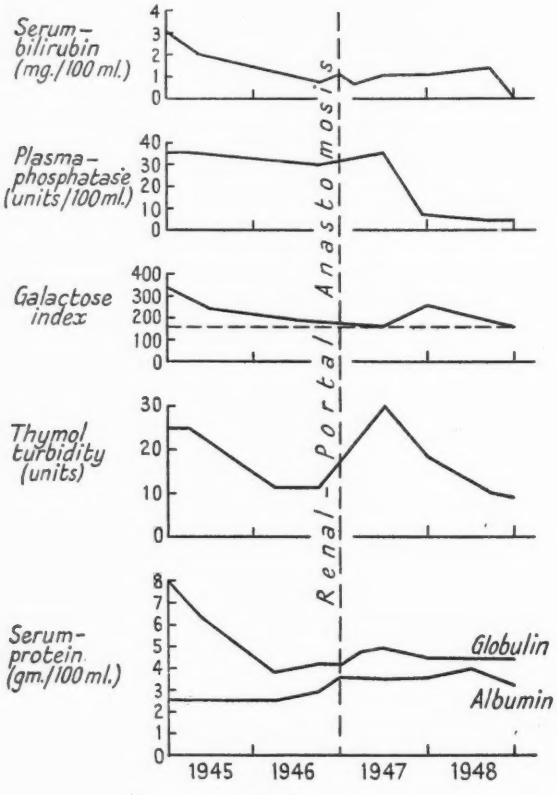

FIG. 2.

recovery eventually occurs, urobilin and urobilinogen reappear in the urine and, in the absence of relapse, remain present until recovery is apparently complete. Pigment reappears in quantity in the faeces, and recovery then follows much the same pattern as in the milder forms of hepatitis already described, although the return of tests to normal may be delayed.

In cases which have progressed to chronic fibrosis after long and persistent, or relapsing, jaundice the galactose and laevulose tolerance tests may remain positive throughout, instead of reverting to normal within 14 days or so of the onset of jaundice. Hippuric acid synthesis remains impaired, but no more so than in acute hepatitis of long duration in which recovery occurs. On the

other hand the flocculation tests remain positive, often strongly so, and frequently the serum-globulin is increased. In one of the author's cases a figure of nine gm. of globulin per 100 ml. was recorded. The plasma-phosphatase level remains high, and often increases to levels usually associated with obstructive jaundice. It is at this stage that death may occur either from haemorrhage associated with portal hypertension, or from intercurrent infection associated with ascites and oedema. Death from liver failure is less common, but when it does occur is heralded by the same features as acute liver failure in any other stage of hepatitis, i.e. hypoglycaemia, aminoaciduria, aminoacidaemia, hypoalbuminaemia, and hypoprothrombinaemia unresponsive to parenteral vitamin K therapy.

Just as the results of liver function tests change during the course of acute hepatitis, they may change during the course of chronic hepatitis. In particular, the results of the flocculation and precipitation tests and the protein-partition determinations may vary greatly during the course of the disease. This is well shown in the case of the patient whose changes in hepatic function during a period of three years are shown in Fig. 2. In this case the serum-globulin fell during the course of 12 months from over eight gm. to a little over three gm. per 100 ml., but after renal-portal anastomosis it rose to about five gm. per 100 ml., and subsequently fell gradually in the course of two years to just over four gm. per 100 ml. With these changes in serum-globulin the thymol turbidity test showed parallel variations, ranging between 24 and 11 units.

Sherlock (1948) has admirably reviewed the subject of post-hepatitis cirrhosis. Among nine cases, she observed three in which there was no clinical or biochemical evidence of abnormality, although histological evidence of cirrhosis was present. Moreover, in one of these cases the cirrhosis was seen to regress. It may well be that cirrhosis, with portal hypertension and hepatic decompensation, can develop after a latent period of years during which all tests of liver function are apparently normal. Until the remote sequelae of the major epidemics of acute hepatitis which reached their height in 1944 have been studied, it is not possible to consider the diagnosis of such cases except by biopsy.

Cirrhosis of the Liver

Patients with cirrhosis of the liver which has developed without a previously recognized acute hepatitis may have had acute hepatitis without jaundice; or their cirrhosis may be due to an entirely different factor or multiple factors. In either event they often present a different picture from that which develops after long and persistent, or relapsing, jaundice. Jaundice is not necessarily present. Tests of glycogenic function usually give normal results, except in the terminal illness of patients dying of liver insufficiency, when the other features of liver failure become manifest. Hippuric acid synthesis may be impaired, but the result of this test is very variable. A fall in the plasma-albumin concentration, with or without a rise in that of plasma-globulin, may be observed. The empirical flocculation tests are often strongly positive, though this result does

not seem to be found so regularly as in post-hepatitis cirrhosis. There is evidence that in cirrhosis the zinc sulphate test of Kunkel (1947) is more frequently positive than the thymol turbidity test (Maclagan, 1950). Serum-phosphatase may also be increased, but to a level less high than that found in post-hepatitis cirrhosis.

The Choice of Tests

It is clear that in assessing the results of liver function tests in acute hepatitis we must take into account the severity and the stage of the disease. Failure to consider these may well explain the discrepancies of the results obtained with similar tests by different laboratories. Some hospitals may admit patients with acute hepatitis only when there is some unusual feature connected with them, either a doubtful diagnosis or a condition of unusual severity. Centres engaged in special research into hepatic function make their requirements known within the area they serve, so that they tend to get a high proportion of early cases. It is therefore not surprising that discrepant results are obtained. There is a striking analogy between nephritis and hepatitis. Just as the tests of greatest value in the second stage of Ellis's type 1 nephritis are wholly different from those which are most useful in the first and third stages, so the tests of liver function which are of greatest value during, and shortly after, the pre-icteric stage of acute hepatitis are quite different from those which are of value when the jaundice has been present for some weeks. The scheme of tests shown on pages 273–4 is proposed as being the most serviceable in diagnosis. In the Appendix are shown the results to be expected from these tests in health and in liver disease. The most generally useful investigation consists of the examination of the urine for pigments. While clinicians are generally familiar with qualitative tests for bilirubin, they do not appear to make use of the simple tests available for urobilin and urobilinogen. Schlesinger's zinc acetate test is the best, since it detects both urobilin and its colourless precursor, urobilinogen. But Ehrlich's test for urobilinogen, performed on *freshly passed* urine, has precisely the same significance, and details of this test are therefore included in the Appendix. In general, it may be said that if urobilin and urobilinogen are present during the early stages of an attack of jaundice the condition is most probably one of acute hepatitis. It is therefore of prime importance that these tests should be carried out early in the course of the disease, when the diagnosis can be reached in most cases without the need of further investigation. It is only when the urine has not been tested during the early stages of the disease that the more complicated tests become necessary. If the urinary tests are not performed until jaundice has become severe (when urobilin and urobilinogen disappear from the urine), and if the other tests give equivocal results, it is most important to investigate the faecal stercobilinogen in order to rule out malignant obstruction. In the author's opinion every case of severe jaundice persisting for six weeks should have had the diagnosis of malignant obstruction ruled out either by clear biochemical evidence or by laparotomy. If laparotomy should prove necessary, the response of the prothrombin time to parenteral vitamin K therapy

should be determined, and no patient should be subjected to laparotomy until the prothrombin time is normal.

The progress of liver disease is most simply followed by *repeated* qualitative tests for *urinary pigments*. These may be supplemented by repeated determinations of serum-bilirubin and, where appropriate, by repeated tests for serum-phosphatase and for thymol and zinc turbidity. It should be observed that these last two tests may not become normal until some time after clinical recovery.

SCHEME OF TESTS FOR DIFFERENT STAGES OF LIVER DISEASE

In all cases serum-bilirubin is estimated to assess the severity of the jaundice.
Class A: essential tests. Class B: tests necessary if the results of A are equivocal.

Acute hepatitis without jaundice.

Class A tests.	Urinary pigments.	Bilirubin present; urobilin and urobilinogen present in later stages.
	Van den Bergh test.	Direct test may be positive with slight or absent hyperbilirubinaemia.
Class B tests.	Galactose or laevulose tolerance.	

Mild jaundice (serum-bilirubin less than about 10 mg./100 ml.) of less than six weeks' duration.

Class A tests.	Urinary pigments.	Bilirubin, urobilin, and urobilinogen present.

Class B tests (if haemolytic jaundice is likely, perform direct van den Bergh reaction, which may be negative; carry out class B tests, which should be negative; confirm with quantitative test of faecal stercobilin).

Serum-phosphatase.
Thymol turbidity.
Zinc sulphate turbidity.

Severe jaundice (serum-bilirubin more than 10 mg./100 ml.) of less than six weeks' duration.

Class A tests.	Urinary pigments.	Bilirubin alone present. Reappearance of urobilin and urobilinogen provides first indication of recovery.
Class B tests.	Serum-phosphatase. Thymol turbidity. Zinc sulphate turbidity.	If the results are equivocal, test for faecal stercobilin to exclude malignant obstruction.

Jaundice of more than six weeks' duration.

Class A tests.	Urinary pigments.	Appearance of urobilin and urobilinogen with early disappearance of bilirubin indicates recovery. Urobilin and urobilinogen disappear when recovery is complete. Persistence of urobilin and urobilinogen, with or without bilirubin, in the urine suggests that recovery is not complete.
	Serum-bilirubin.	If the condition is progressing to chronic fibrosis the serum-bilirubin may fluctuate over a wide range of values; with recovery it usually falls gradually to normal levels.
	Serum-phosphatase.	
	Thymol turbidity.	
	Zinc sulphate turbidity.	
Class B tests.	Serum-albumin and -globulin.	
	Laevulose or galactose tolerance.	If impaired, the condition may progress to chronic fibrosis.

Post-hepatitis fibrosis and cirrhosis of unknown aetiology.

Class A tests.	Urinary pigments.
	Serum-bilirubin.
	Thymol turbidity.
	Zinc sulphate turbidity.
	Serum-phosphatase may be elevated to levels usually associated with obstructive jaundice.
Class B tests.	Serum-albumin and -globulin.
	Coproporphyrin in urine.

The tests of glycogenic function are of limited value, not because they are ineffective in testing the appropriate function, but because the rapid regeneration of liver tissue results in an early recovery of this function in all but very progressive liver disease. The hippuric acid synthesis test is not included in the suggested scheme because it frequently gives positive results in obstructive jaundice and because, as has been explained earlier, the results are in no way parallel to the severity of the liver disease.

APPENDIX

1. *Ehrlich's Test for Urobilinogen*

Add 1 ml. of Ehrlich's aldehyde reagent (3·3 gm. *p*-dimethylaminobenzaldehyde in 10 per cent. w/v hydrochloric acid) to 10 ml. of *fresh undiluted urine* and allow to stand three minutes. A red colour is positive for urobilinogen.

2. *Interpretation of Tests*

Test	*Normal values*	*Values found in liver disease*
Serum-bilirubin (Malloy and Evelyn, 1937)	Less than 0·75 mg./100 ml.	More than 0·75 mg./100 ml. in hyperbilirubinaemia.
Serum-phosphatase (King, 1946)	4–13 units/100 ml.	13–35 units/100 ml. in many cases of hepatitis. Over 35 units/100 ml. in most cases of obstructive jaundice and in some cases of cirrhosis.
Thymol turbidity (Maclagan, 1944 *a*)	Less than 4 units	Over 4 units
Zinc sulphate (Kunkel, 1947)	Less than 4 units	Over 4 units
Laevulose tolerance (Thompson and Wilkinson, 1940)	Increase in blood-laevulose not above 15 mg./100 ml., returning to below 10 mg./100 ml. within 2 hours	Increase in blood laevulose above 15 mg./100 ml., failing to return to below 10 mg./100 ml. within 2 hours
Galactose tolerance test (Maclagan, 1940)	Galactose index (the sum of the first 4 half-hourly galactose levels) less than 160	Galactose index more than 160
Serum-albumin (Harrison, 1947)	3·4–6·7 gm./100 ml.	Less than 3·4 gm./100 ml. in acute necrosis, in long standing hepatitis and in cirrhosis
Serum-globulin (Harrison, 1947)	1·2–2·9 gm./100 ml.	More than 2·9 gm./100 ml. in long standing hepatitis and in cirrhosis

Summary

The more commonly employed tests of liver function are critically discussed. The results of these tests vary according to the severity and stage of the liver disease. In the pre-icteric stage of acute hepatitis, bilirubinuria and the development of a positive direct van den Bergh reaction may be the earliest sign. A little later, urobilin and urobilinogen appear in the urine, and glycogenic function appears to be impaired. When jaundice develops, glycogenic function usually returns rapidly to normal, but may remain impaired in cases progressing to chronic fibrosis. Serum-phosphatase increases with the development of jaundice in acute hepatitis, but not usually to levels associated with obstructive jaundice. The flocculation tests appear to become positive as regeneration of liver tissue occurs. Of the various tests, the simple qualitative test for urobilinogen is the most useful if carried out sufficiently early in the history of the disease. If jaundice has become so severe that this test is negative, then other tests, such as that of serum-phosphatase, the thymol turbidity reaction of Maclagan, and the zinc sulphate test of Kunkel become necessary. Acute hepatitis when not investigated early may be difficult to diagnose from malignant obstruction, and estimation of faecal stercobilinogen may then assist in diagnosis. In post-hepatitis cirrhosis the glycogenic function is often diminished, serum-phosphatase is often greatly increased, and the flocculation tests, especially the zinc sulphate and thymol turbidity reactions, are usually positive. In other forms of cirrhosis the biochemical findings are often more variable.

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616.61–003.7:616.152.13

NEPHROCALCINOSIS ASSOCIATED WITH HYPERCHLORAEMIA AND LOW PLASMA-BICARBONATE[1]

By A. D. TELFORD GOVAN

(From the Research Department, Glasgow Royal Maternity and Women's Hospital)

With Plates 23 to 26

The following pathological report deals with a case of nephrocalcinosis of which full clinical details were reported by Baines, Barclay, and Cooke in this journal (1945).

Clinical Summary

The patient, an adult female 29 years of age, was first seen at the Queen Elizabeth Hospital, Birmingham, in 1940 on account of renal colic. She had had polyuria and thirst since the age of 10 years. There were no symptoms of renal infection, and the patient had never taken excessive amounts of vitamin D. For a number of years she had felt soreness at the corners of the mouth during the winter, and she had had a sore tongue for two years. Her father had died of renal stones, but the other members of the family were healthy. The patient was seen at intervals during the next two or three years, during which she had several attacks of colic, and passed small calculi. She was in hospital on a number of occasions, and a full clinical and biochemical investigation was made. She was moderately well built. No abnormality could be detected in her skin. Her teeth were in good condition, and nothing abnormal was found in her heart, lungs, or central nervous system. Her blood-pressure was 110/70 mm. Hg. X-ray examination in 1940 showed numerous stones in both kidneys. The renal pelves did not seem to be dilated, and no evidence of decalcification could be seen in X-rays of the femur, humerus, pelvis, tibiae, or skull. The sella turcica was normal. Examination of the urine revealed small amounts of albumin, a few red cells and occasional pus cells. Bacteriological examination, repeated at intervals, was negative, and no evidence of tuberculosis was found after inoculation of guinea-pigs. The pH of the urine varied between 6·7 and 7·1. A ketogenic diet plus large doses of ammonium chloride failed to depress the pH below 6·3. The urea clearance in 1940 was found to be 45 per cent. of normal. A detailed analysis of the urinary excretion showed that the pH and specific gravity of the urine were fixed throughout the whole 24 hours. Relatively large doses of sodium-citrate-citric-acid mixture produced no appreciable change in the pH, although the phosphate output was greatly increased. Ammonia excretion was low. There was no sign of glycosuria at any time. Her

[1] Received January 25, 1950.

blood picture was normal. The blood urea varied between 35 and 45 mg. per 100 ml. Serum-calcium was 11 mg. per cent., serum-phosphorus 1·8 mg. per cent., and serum-phosphatase 8 units. The plasma CO_2-combining power was low (32 vols. per cent.). There was well-marked hyperchloraemia, and the plasma-proteins were raised. Although the sodium-citrate-citric-acid mixture produced little change in the pH of the urine, its steady administration caused the acid-base balance of the blood to approach normal values, and the serum-proteins fell. The serum-phosphorus rose, the calcium diminished, and alkaline phosphatase activity increased. Calcium balance tests showed that, on a dietary intake of 457 mg. calcium, there was a negative balance of 387 mg. of calcium daily. Chemical analysis and examination by the X-ray diffraction method showed that the renal calculi were identical in composition with 'dahlite' and could not, therefore, be distinguished from bone.

The patient remained well, apart from one attack of renal colic in May 1943, until April 1945, when she developed a respiratory infection. Death occurred in a few days, and appeared to be due to a severe reaction to sulphathiazol.

Post-mortem Findings

The subject was an adult female of slim build. There were no significant external abnormalities, although the body appeared to be extremely pale. The heart weighed 280 gm. and was of average size. The myocardium was pale, but quite firm and of good texture. No abnormality could be found in the valves or coronary arteries. Both lungs were bulky, especially the right. Over the pleural surface at both bases there was a well-marked fibrinous exudate, and there was a slight excess of fluid in the cavities. The right lower and middle lobes showed diffuse consolidation, with small points of suppuration. On the left side consolidation was patchy, and confined to the lower lobe. The liver was enlarged, weighing 1,500 gm. Its parenchyma was pale, lobular markings blurred, and consistency rather soft. The gall-bladder was normal. No significant change could be seen in the spleen, which weighed 150 gm.

Both kidneys (average weight 250 gm.) were enlarged. The capsules stripped easily, leaving a smooth surface. There was marked congestion of the stellate veins, but the intervening renal tissue was very pale. There was great dilation of the pelves, which contained numerous round, light-brown calculi of varying size. The calyces were dilated and ended in large bulbous expansions, most of them half an inch in diameter. These contained either single large stones of a light-brown colour, which completely filled the expanded calyces, or innumerable tiny calculi of the same colour varying in diameter from $\frac{1}{16}$ to $\frac{1}{4}$ of an inch (Plate 23, Fig. 1). The mucous membrane of many of the calyces was eroded, and the space was partly lined by rough ulcerated renal parenchyma. The outer cortical tissue was very pale, and the normal markings blurred, but there was marked congestion of the medulla and inter-pyramidal cortex. A few haemorrhages were present in this zone. At several points the cortical tissue was thinned almost to vanishing-point by the dilatation of the calyces. Cortical thinning was especially marked at both lower poles (see Plate 23, Fig. 1). Both ureters were

dilated and thick-walled. Stones were present on both sides; obstruction was only partial on the left side, but complete on the right. The terminal two and a half inches of the right ureter were filled by a column of impacted smooth, shiny, brown stones, the average diameter of which was $\frac{1}{4}$ of an inch (Plate 23, Fig. 2). About four inches above this column was another, approximately an inch and half in length, consisting of fewer and more loosely packed stones of the same type as those in the kidney. On the left side there were only a few very small loose stones at various levels in the ureter. The bladder mucosa showed a mild inflammatory reaction, with occasional petechiae.

No abnormality was found in the uterus or its appendages. The stomach and intestines appeared to be normal. There was no enlargement of the parathyroid glands. The thyroid and suprarenal glands were healthy. There was no sign of abnormality in the pancreas. There was no naked-eye evidence of decalcification of the bones. Unfortunately permission to examine the brain was withheld.

Histology

The material for microscopic examination was fixed in 10 per cent. formol-saline. Pieces were selected from the lungs, liver, spleen, kidneys, and parathyroids. Paraffin and frozen sections were prepared and stained with haematoxylin and eosin, Dunn's aniline-blue orange-G, Masson's trichrome, Gram's method, and Sudan IV.

Lung. Three types of reaction are apparent in the lung tissue. There is widespread oedema, and in the oedematous alveoli are large numbers of macrophages, a few of which contain granules of brown pigment. In other parts there are a number of adjoining alveoli containing dense masses of fibrin. Practically no cell-reaction can be seen, either in the fibrin plugs or in the alveolar walls. Quite apart from these areas are others showing an acute inflammatory reaction, with numerous polymorphonuclear cells filling the alveoli. In a few places early suppurative changes are in progress, with destruction of the alveolar walls. The associated bronchi show a marked inflammatory reaction, with desquamation of epithelium and much polymorphonuclear infiltration of the wall and basement membrane. Small masses of gram-negative bacteria, having the appearance of *Micrococcus catarrhalis*, are present in these areas. The pleura is thickened, and there is early organization of the fibrinous exudate on the surface. *Liver.* There is a slight fatty deposit in the cells near the portal tracts, but otherwise the liver appears to be normal. The portal veins are congested, and one small tributary contains a fibrinous thrombus with a considerable number of polymorphonuclear cells. *Spleen.* There is marked congestion of the splenic sinusoids, and the sinusoidal endothelial cells are swollen and active in appearance, but there is no evidence of any gross lesion. *Parathyroids.* There is no evidence of hyperplasia in these glands.

Kidney. The glomeruli are much enlarged. This is mainly due to dilation of the capillaries. There is no sign of increased cellularity, and the appearances are not those of a glomerulitis. There is thickening of the walls of individual

capillary loops in most of the superficial glomeruli (Plate 24, Fig. 3). In contrast to this, deeper glomeruli show a marked thickening of the whole tuft (Plate 24, Fig. 4), and in addition many glomeruli have undergone hyaline obliteration. Only a few superficial glomeruli are hyalinized, but there is marked thickening, and in some cases reduplication, of the basement membranes of Bowman's capsules (Plate 24, Fig. 4). There is thickening of the basement membrane of all the cortical tubules. This fibrosis is especially marked around some of the second convoluted tubules (Plate 25, Fig. 5), and is intense around the medullary portions of the narrow and ascending limbs of the loops of Henle. A generalized change is present in the epithelium lining the first convoluted tubules. The cells are greatly swollen and grotesque in form, owing to the presence of large vacuoles of various shapes. Nuclei are pushed to the base of the cells. In some instances the changes are so extreme that the whole tubule presents the appearance of a foam of vacuoles. Although in some areas the cells appear to be comparatively healthy despite vacuolation, in others there is marked desquamation, and many of the cells are obviously necrotic (Plate 25, Figs. 6 and 7). In a few places the nuclei have disappeared, and only vacuolated cytoplasmic masses remain. Many tubules show appearances of regeneration. The epithelium in these cases has changed its morphological character. Usually it takes the form of a flat ribbon of hyperchromic cells, some of which are undergoing mitotic division (Plate 26, Fig. 8), but occasionally the epithelium is heaped up on one aspect of the tubule-wall as a multinuclear syncytial mass. The cytoplasm of these regenerating cells is basophilic. All these changes, degenerative and regenerative, can be traced down the whole length of the descending portion of the first convoluted tubule. Calcification of necrotic cells is present (Plate 26, Fig. 9), but this only occurs in isolated tubules, and is not a prominent feature. It is difficult to identify the narrow portion of Henle's loops owing to the intense fibrosis. Many are reduced to mere slits in the fibrous tissue. Granular debris is present in some. The broad ascending limbs of Henle tend to be dilated. Many contain casts, some of which show early calcification (Plate 26, Fig. 10). In general the epithelium appears to be in a healthier state than that of the first convoluted tubules, but necrosis is present in some tubules, and the necrotic epithelium is undergoing calcification.

More marked changes can be seen in the collecting tubules. Calcification is common, but in most cases the appearances suggest that it is a calcification of the contents rather than of the lining epithelium itself. In some areas, however, definite calcification of necrotic epithelium is occurring. Calcified masses can also be seen lying embedded in the surrounding fibrous tissue. This may be due in some instances to calcification occurring primarily in the interstitial tissue, but in most cases histological examination suggests that the calcified material is extruded from the tubules by a process of epithelial regeneration extending over one of its surfaces, thus excluding it from the reconstituted lumen (Plate 26, Fig. 11). The ducts of Bellini also contain calcified material. Many of them show ulceration, and there is a marked inflammatory reaction in the surrounding tissue, with pus formation. This inflammatory reaction may

be responsible, in part at least, for the fibrosis surrounding the medullary portions of the cortical tubules. The inflammation also involves the pelvis of the kidney, and the pus contains scanty gram-positive cocci.

Many of the branches of the renal artery show fibrosis of the media, and some of the afferent arterioles of the glomeruli are almost obliterated. The latter supply glomeruli which show varying stages of hyalinization, and the changes are most marked in the juxta-medullary region. There is some congestion of the veins, especially in the cortex.

Bone. Although no sign of bony change was found at post-mortem, histological examination of the femur showed definite decalcification of the shaft.

Discussion

This syndrome has been recognized for a considerable time. Excess of vitamin D has been suggested as a possible cause (Putschar, 1929; Thatcher, 1931), but subsequent authors have rejected this theory. Lightwood, Maclagan, and Williams (1936) showed that these patients suffer from persistent acidosis. Extensive biochemical investigations of such cases were made by Butler, Wilson, and Farber (1936), and by Albright, Consolazio, Coombs, Talbott, and Sulkowitch (1940). Similar investigations in the present case were made by Baines, Barclay, and Cooke (1945). From the reports of these authors it seems that the main features of the disease are persistent acidosis with hyperchloraemia, low serum inorganic phosphate and normal serum-calcium, and polyuria, with a urine of fixed specific gravity, low acidity and diminished ammonia content.

Although complete clinical surveys have been made in these cases, the pathological descriptions are lacking in detail. Most of the histological reports are very short and are concerned mainly with calcium deposits in the renal medulla. Nevertheless, recent reports suggest that there is a renal defect, and Albright and his colleagues suggested that the kidney is unable to excrete an acid urine and to form ammonia. In the present case the structure of the parathyroids was quite normal, and this, together with the alterations in serum-calcium produced by treatment, indicates that the excessive mobilization of calcium was not due to over-activity of these glands. Unfortunately it was impossible to examine the pituitary, but there was no clinical evidence that it was hyperactive. No doubt the renal lesions were associated with the biochemical changes. There is an obvious relationship between the excretion of calcium and the formation of calculi. Previous observers have stated that deposition of calcium takes place both within the tubules and in the surrounding connective tissue (Butler, Wilson, and Farber, 1936). In the present instance, however, it seems likely that calcification first affected the casts or the necrotic epithelial cells, and that the resulting mass subsequently ulcerated through the wall of the tubule and was gradually extruded.

It is much more difficult to relate the other pathological changes to the clinical condition. The marked degree of secondary renal change in this case, especially the medullary fibrosis, must have altered circumstances considerably.

There is reason to believe, however, that the gross vacuolation in the first convoluted tubules was of some aetiological significance. That this change was of a chronic nature is shown by the presence, in some tubules, of a low hyperchromic form of epithelium. This kind of epithelium was demonstrated by MacNider (1944) in dogs with chronic renal deficiency, and he further showed that it is much more resistant to toxic substances than normal renal epithelium. This suggests that the preceding stage of vacuolation, in the present case, eventually led to degeneration. The nature of the vacuoles, and the reason for their existence, is not apparent, but they may have been related to the exchange of phosphorus, which has been shown to occur mainly in the first convoluted tubules (Walker, Bott, Oliver, and MacDowell, 1941; Pitts and Alexander, 1944). Treatment did not alter the raised blood-chloride or the low acidity of the urine. These two factors, and the low output of ammonia, appear to be a fundamental part of the syndrome. Recent studies indicate that the reabsorption of chloride (Walker, Hudson, Findley, and Richards, 1937), the acidification of urine (Montgomery and Pierce, 1937) and the formation of urinary ammonia (Walker, 1940) are functions of the distal nephron. In the present case a marked fibrosis involved the distal portions of many nephrons. This was obviously in the nature of a secondary change, but whether secondary to inflammation following calculus formation, or to some previous change in the tubules, is not clear. Fibrosis certainly occurred in areas at some distance from the pelvic inflammation.

My thanks are due to Drs. W. T. Cooke, J. A. Barclay, and G. H. Baines for permission to make use of the hospital records of this case.

Summary

1. The pathological features are described of a case of nephrocalcinosis with persistent hyperchloraemia and low plasma-bicarbonate.

2. The most marked feature was a gross degree of vacuolation of the epithelium lining the first convoluted tubules of the kidneys. This change appeared to be chronic and may have had aetiological significance.

3. An intense fibrosis involved the medullary structures, including many of the limbs of Henle. Much of this was secondary to calculus formation and inflammation.

4. Calcium was deposited mainly in casts and necrotic tubular cells.

5. Many of the smaller calculi, originally formed within the tubules, ulcerated the tubular walls and were eventually extruded, thus coming to lie in the surrounding connective tissue.

6. There was no pathological evidence that the syndrome was due to overactivity of the parathyroid glands.

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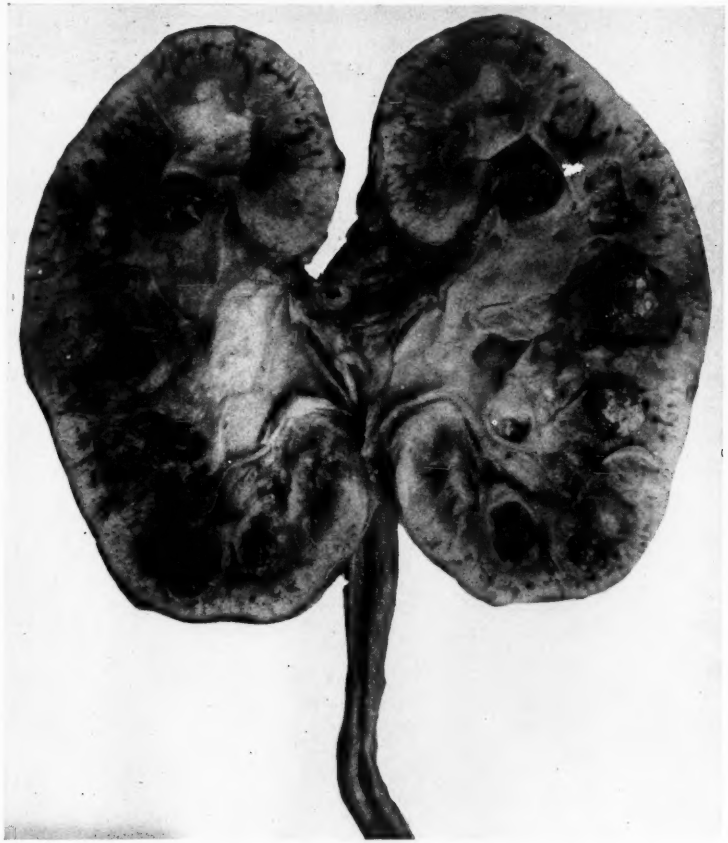

FIG. 1. Right kidney. The appearances on the left side were similar

FIG. 2. Bladder and lower end of both ureters. Note the column of stones in the right ureter

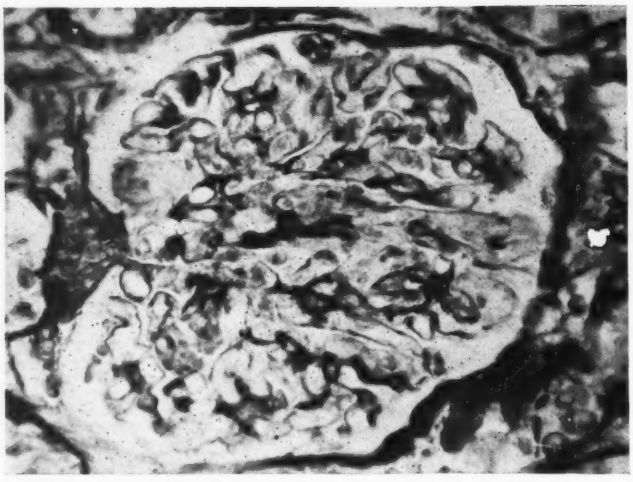

FIG. 3. Superficial glomerulus, showing thickening of the basement membrane of some capillary loops (aniline blue, orange G, × 450)

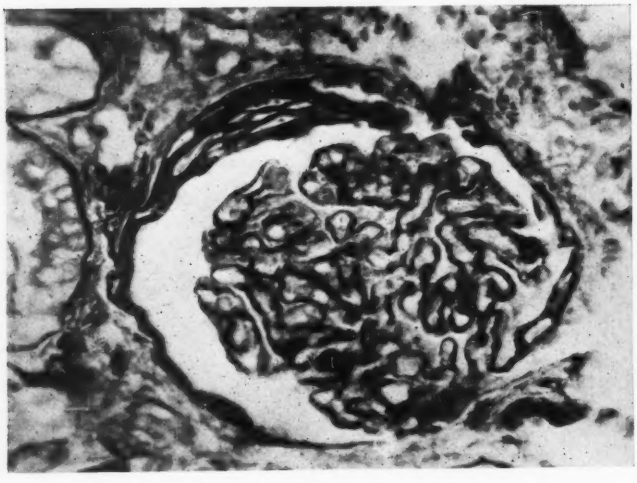

FIG. 4. Deep glomerulus, showing thickening of the walls of all capillary loops. Note reduplication of the basement membrane of Bowman's capsule (aniline blue, orange G, × 450)

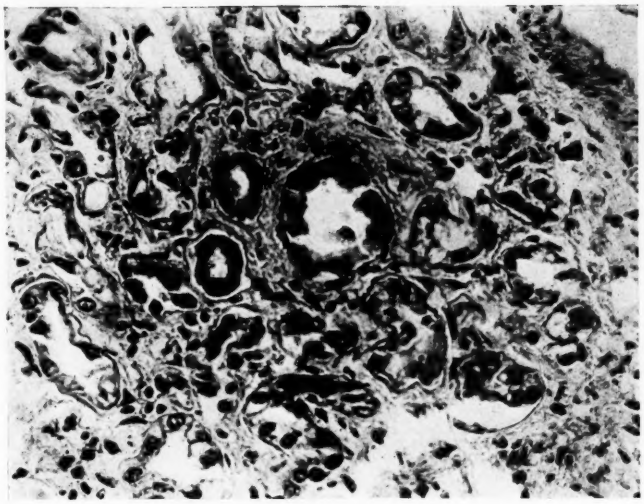

FIG. 5. Localized area of fibrosis around a second convoluted tubule (haematoxylin and eosin, × 320)

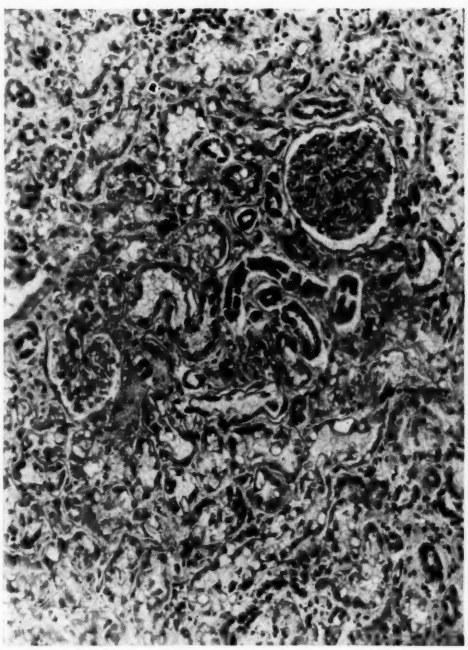

FIG. 6. Low-power view of cortex, showing generalized vacuolation of the epithelium of the first convoluted tubules (haematoxylin and eosin, × 60)

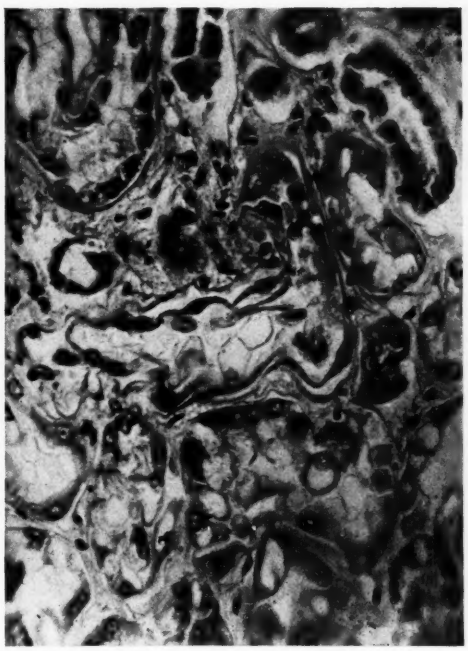

FIG. 7. High-power view of cortical tubules (haematoxylin and eosin, × 320)

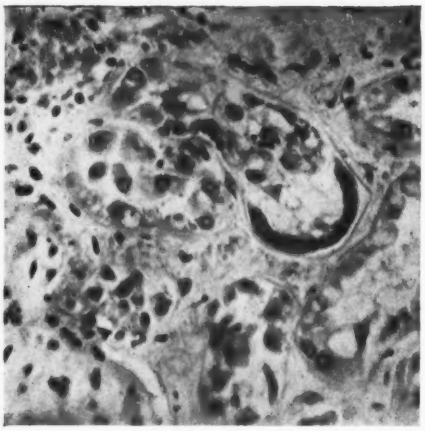

FIG. 8. First convoluted tubule, showing low hyperchromatic type of epithelium formed during regeneration (haematoxylin and eosin, × 230)

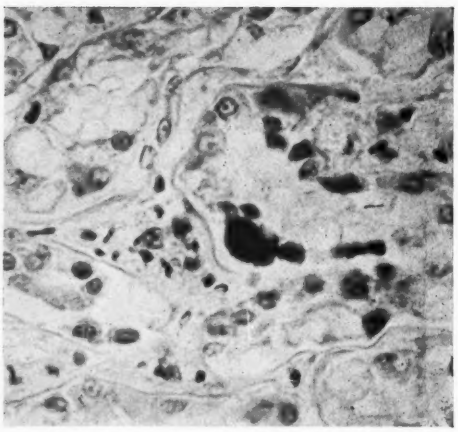

FIG. 9. Showing calcification of a single cell in the lining epithelium of a first convoluted tubule (haematoxylin and eosin, × 320)

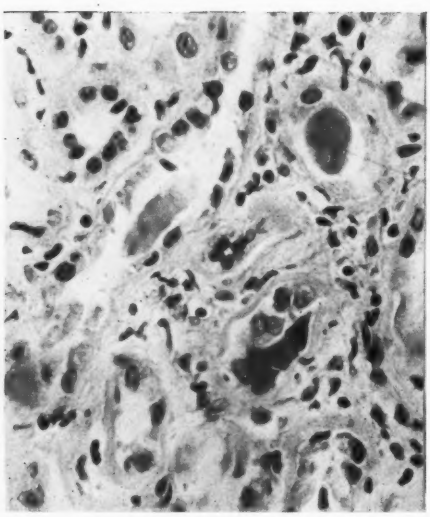

FIG. 10. Second convoluted tubules, showing varying degrees of calcification of casts and of epithelial cells (haematoxylin and eosin, × 320)

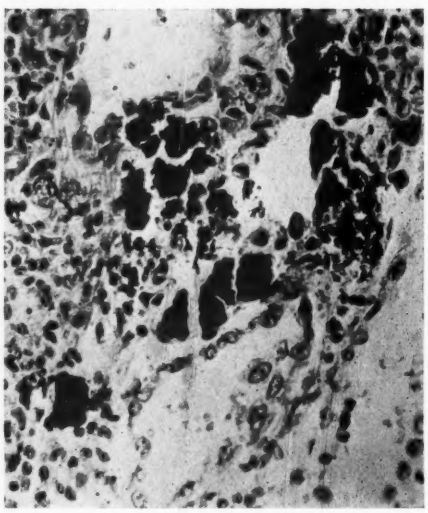

FIG. 11. Showing masses of calcified material which have been extruded from the collecting tubules (von Kossa's stain, × 230)

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IDIOPATHIC HYPERCHLORAEMIC RENAL ACIDOSIS OF INFANTS[1]

(NEPHROCALCINOSIS INFANTUM)

OBSERVATIONS ON THE SITE AND NATURE OF THE LESION

By ALBERT L. LATNER and ERIC D. BURNARD

(From the Departments of Chemical Pathology and Child Health, King's College, Newcastle-upon-Tyne)

With Plate 27

A form of chronic acidosis apparently of renal origin is known to cause intermittent vomiting and dehydration, as well as a general failure to thrive, in certain infants. Biochemical investigation reveals a raised plasma-chloride in addition to the lowered alkali reserve; the blood-urea concentration is generally normal in the absence of dehydration. The plasma inorganic phosphorus is normal or slightly reduced. The urine is usually alkaline to litmus (Payne, 1948). The natural course of the disease is by no means completely known. Most cases described in the literature have been fatal, with calcification in the renal tubules at necropsy (Lightwood, 1935; Anderson, 1939; MacGregor, 1948; Butler, Wilson, and Farber, 1936; Peterman, 1945; Boutourline-Young, 1949). Recoveries have been reported (Lightwood, 1936; Hartmann, 1939–40; Stapleton, 1949) and the illness in such cases has run a course of some months. Renal calcification has seldom been demonstrated during life in infancy, but in adults with comparable features of chronic acidosis and polyuria calcification has been seen in radiographs of the kidney region (Albright, Burnett, Parson, Reifenstein, and Roos, 1946; Baines, Barclay, and Cooke, 1945; Greenspan, 1949). The normal values of urea clearance and dye excretion obtained in these older subjects have been emphasized, as has their good response to treatment with alkalis.

There is general agreement that a disturbance of renal function is responsible for the acidosis and associated phenomena, but histological findings are not helpful in explaining the site or nature of the defect. The many causes of renal calcification reviewed by Greenspan (1949) render the pathologist's task the more difficult. When patients with the accepted clinical and biochemical features of this disease come to post-mortem examination, renal calcification is generally present, especially in relation to the second convoluted and collecting tubules. In a minority, however, there has been no calcification (Albright, Burnett, Parson, Reifenstein, and Roos, 1946). Histological evidence

[1] Received March 30, 1950.

of inflammation is usually absent or slight. Rarely, degenerative changes in the proximal tubules have been described (Baines, Barclay, and Cooke, 1945).

There is a singular association in these patients of systemic acidosis with a urine that is alkaline or, at best, weakly acid. The low urinary output of ammonia and the failure to eliminate a test dose of acid-producing salt, in the presence of otherwise normal renal function, suggested that the primary defect was failure of the second convoluted tubule to eliminate acid (Albright, Burnett, Parson, Reifenstein, and Roos, 1946). The calcium precipitation was held to be the consequence of an increased concentration of this ion, owing to acidosis, in a tubular fluid of higher pH than normal. It was suggested that the cellular damage resulting from deposition of calcium explained the polyuria and the low specific gravity of the urine. On the other hand, the finding of a high concentration of bicarbonate in the urine suggested that an alternative cause of the acidosis might be incomplete reabsorption of this substance (Hartmann, 1939–40; Stapleton, 1949). This, in the light of recent work (Pitts and Lotspeich, 1946; Pitts, Ayer, and Schiess, 1949), would in our opinion place the defect in the proximal tubule. Pitts and his associates have shown that sodium bicarbonate is absorbed in the proximal and distal convoluted tubules. The proximal absorption is such as to maintain ionic neutrality, and its mechanism is by no means understood. In the distal tubule exchange occurs between sodium ions in the tubular fluid and hydrogen ions derived from the carbonic acid in the tubule cells. The sodium bicarbonate thus formed within the cells is absorbed into the blood-stream. Within the lumen of the tubule, the replacement of sodium ions of disodium phosphate by hydrogen ions results in the formation of monosodium dihydrogen phosphate, acidifying the urine, while the sodium bicarbonate becomes converted to carbonic acid, and contrary to the views of Gamble (1922) the partial pressure of carbon dioxide in the urine becomes raised above that in the plasma. The whole mechanism results in conservation of sodium for bodily economy and at the same time produces the free acid in the urine. Pitts, Ayer, and Schiess (1949) have shown that in normal individuals in whom acidosis has been induced all the bicarbonate present in the glomerular filtrate is absorbed in the proximal tubule. The presence of bicarbonate in the urine of patients suffering from idiopathic hyperchloraemic acidosis would therefore suggest a faulty absorption in this portion of the nephron.

If these views be accepted, it is possible to explain the poor excretion of ammonia and free acid in nephrocalcinosis infantum as the result of poor absorption of bicarbonate in the proximal tubule, rather than as a primary fault in the distal tubule. It has been shown that there is a form of competition between the bicarbonate and disodium phosphate for the hydrogen ions supplied by the distal tubular cells. Under conditions of normal phosphate concentration, the presence of bicarbonate in the distal tubule would thus result in a subnormal production of free acid and ammonia (Pitts, Lotspeich, Schiess, and Ayer, 1948; Pitts, Ayer, and Schiess, 1949). If the phosphate concentration could be artificially raised much above normal, phosphate might play the major part in the competition, and increased production of free acid, and possibly of

ammonia, would result. A response of this type would point to the distal tubular mechanism being normal. These considerations led us to attempt to identify the site of the tubular defect in the disease under consideration by the methods previously used for investigating acid secretion and base conservation in the normal kidney (Pitts and Alexander, 1945; Pitts, Lotspeich, Schiess, and Ayer, 1948). We believe the use of these methods has been justified by the findings. As a result of an infusion of sodium phosphate the kidneys in our patients were found to be capable of secreting free acid to a degree comparable with controls, and of significantly increasing the output of ammonia. Urinary bicarbonate excretion was excessive in the resting state, but from evidence provided by the partial pressure of carbon dioxide in the urine it was deduced that the distal tubule was reabsorbing bicarbonate in a normal manner, and that the proximal tubule was the site of faulty absorption.

Procedure

Infusion and sample-collection. Under light sedation with paraldehyde, six patients with idiopathic hyperchloraemic renal acidosis and five control patients were catheterized, and the catheter left *in situ*. The urine was collected under paraffin for two hours. An isotonic solution, made up with disodium hydrogen phosphate and monosodium dihydrogen phosphate in the proportion of four to one and with a pH of 7·4, was then infused intravenously for three hours, at the rate of 0·5 to 2 ml. per minute according to age. After an hour's infusion a second two-hour urine collection was made. Blood was withdrawn in paraffined syringes from the internal jugular vein half-way through each urine collection, and the plasma was separated immediately by centrifuging under paraffin in tubes containing potassium oxalate. The specimens were analysed as soon as possible. Streptomycin was given for 36 hours to prevent urinary infection and, except in Case 3, drinks were supplied overnight to ensure an adequate urinary flow.

The controls were suffering from conditions not likely to affect kidney function, and were chosen with the intention of matching the patients by age. They were rendered acidotic with five to eight gm. of ammonium chloride administered during the 18 hours preceding the investigation. The first three were a hydrocephalic infant and two children with arrested tuberculous meningitis. As the procedure appeared virtually free from ill effects, it was considered justifiable to extend the investigation to healthy or almost healthy children. A patient convalescent from mild coeliac disease and another convalescent from an operation for hernia were chosen. In the last control and the last two patients the thiosulphate clearance was estimated by a single injection technique (Newman, Gilman, and Philips, 1946). An intravenous drip was set up and sodium thiosulphate, one gm. per 10 lb. body-weight, was injected in a 10 per cent. aqueous solution over a 15-minute period. The infusion was then maintained with 0·2 N. saline at a rate of 0·5 ml. per minute. Three blood samples were taken at approximately half-hourly intervals commencing 20 minutes from the end of the thiosulphate injection. The first two-hour urine collection was begun at the

same time as the first blood was taken. When the urine sample had been collected, the saline was stopped and phosphate solution infused at 0·5 ml. per minute. This infusion was interrupted after 25 minutes for a second thiosulphate injection over a period of 15 minutes, and then continued for the remainder of the three-hour period. The blood and urine samples were collected as before, commencing 20 minutes after the end of the thiosulphate infusion. There were two minor variations from the general plan. In the first patient investigated, the second urine collection was started at the same time as the phosphate infusion. The results obtained will be seen to differ little from the other cases, but it was realized that it would be preferable to allow an interval for conditions to become stable with regard to acid and ammonia production. In the first control the phosphate solution was delivered at the faster rate of four ml. per minute. This explains the remarkably high level of free acid production which resulted.

A rise of the pulse and respiration rates occurred during the infusion of phosphate, both in patients and in controls. There was considerable thirst for eight to twelve hours. A slight albuminuria was present for two or three days. The serum-phosphorus was measured after 24 hours on three occasions, and was found to be normal. No tetany occurred. Calcium gluconate was none the less given as a routine after the procedure in most instances.

Chemical methods. The pH of the mid-period blood samples and specimens of urine was determined with a Cambridge pH-meter, using a glass electrode. Unfortunately it was impossible, with the instrument available, completely to avoid contact with the atmosphere. Measurements were therefore made as rapidly as possible. By a process of extrapolation of the pH variation with time, it was determined that the error of measurement in the case of plasma was in the neighbourhood of 0·1 pH unit; in the case of urine it was negligible. The bicarbonate content and the partial pressure of carbon dioxide in each plasma and urine sample were calculated from the total carbon dioxide content (Van Slyke and Neill, 1924) using the Henderson-Hasselbalch equation or appropriate nomograms (Sendroy, Seelig, and Van Slyke, 1934; Van Slyke and Sendroy, 1928). The slight inaccuracy in measuring the plasma pH had little effect on the calculated bicarbonate concentrations, but a somewhat more marked effect on the calculated partial pressure of carbon dioxide. The findings in this respect must therefore be regarded with some reserve. The urinary free acid was determined by titration against standard alkali to a pH of 7·35 (Pitts and Alexander, 1945). The blood and urine samples were also analysed for urea, chloride, and phosphate, and the urine for ammonia, by standard laboratory procedures.

Results

The results obtained are shown in Tables I and II. For the most part, glomerular filtration rates were calculated from the urea clearances, using the factor 1·67 (Rubin, Bruck, and Rapoport, 1949). It is recognized that in this manner only approximate values are obtained, but it was felt in the early phase of this investigation that there was not yet sufficient justification for subjecting

these children to the rigours of a more accurate method of direct determination. However, it soon became obvious that the results did justify such procedures, at least in a limited number of investigations. As already indicated, the thiosulphate clearance was therefore determined in Cases 5 and 6 and in Control 5. In these instances the results shown in Table II are calculated from thiosulphate

TABLE I

Urinary Excretion of Ammonia, Free Acid, and Phosphate

In each subject the upper horizontal line of figures refers to data before phosphate infusion, and the lower to data after infusion was commenced. Excretion and absorption values in this and the following table are corrected to 1·73 sq. m. body-surface area.

		Plasma			*Urine*			
Subject	*Urine flow (ml./min.)*	*PO_4 (mM/L).*	*Total CO_2 (mM/L.)*	*pH*	*PO_4 excretion (mM/2 hrs.)*	*pH*	*NH_3 excretion (mM/2 hrs.)*	*Free acid excretion (mEq/2 hrs.)*
Case 1	2·18	1·8	13·4	7·13	2·6	6·55	1·51	1·1
	4·13	8·3	12·9	7·30	37·8	5·80	5·83	25·3
Case 2	3·92	1·1	18·0	7·24	2·7	6·55	5·78	3·3
	3·96	8·3	19·3	7·37	43·2	5·25	13·5	67·2
Case 3	1·20	1·3	9·7	7·34	4·0	6·80	5·64	0·9
	2·65	5·8	16·0	7·38	62·3	5·24	14·4	49·1
Case 4	2·25	1·7	15·9	7·34	3·4	6·27	7·20	2·9
	6·45	7·0	17·3	7·50	57·5	5·76	26·3	29·4
Case 5	1·94	1·4	10·4	7·30	5·4	6·40	4·20	3·7
	2·70	7·0	9·2	7·25	8·3	5·13	19·8	12·3
Case 6	2·25	0·9	9·6	7·28	0·97	6·91	7·13	1·1
	3·35	2·5	11·7	7·24	11·0	5·09	11·9	13·2
Control 1	1·65	0·6	7·0	7·09	5·1	4·66	15·5	8·1
	4·60	12·1	12·5	7·25	163·0	4·80	11·5	140·0
Control 2	2·60	1·4	17·9	7·19	3·0	4·82	14·0	4·3
	2·90	5·8	18·7	7·43	62·6	4·36	8·43	51·0
Control 3	2·94	1·1	19·6	7·22	2·8	4·61	6·99	4·9
	4·18	6·0	22·5	7·50	54·2	4·60	8·12	54·5
Control 4	3·55	1·3	10·6	7·26	7·2	4·88	17·0	9·8
	4·23	8·6	10·1	7·26	52·3	4·74	16·6	37·8
Control 5	1·62	1·1	17·1	7·26	3·2	4·64	8·48	6·4
	2·28	2·9	15·9	7·38	19·2	4·41	13·7	27·8

clearances. It should be pointed out, however, that calculation from the urea clearance did not in any way render the findings less reliable. The filtration rate was used only to calculate the bicarbonate absorption for each 100 ml. of glomerular filtrate. Remarkably little difference in the absorption, expressed in this manner, would result from multiplying the urea clearance by a factor of 3 instead of 1·67, thus covering the recognized range (McCance and Young, 1941). This is because a higher factor indicates a higher filtration rate and, at the same time, a proportionately higher total absorption. The absorption expressed as an amount for a given volume of glomerular filtrate is therefore not significantly affected by the factor chosen. It is satisfying to note that the more exact procedure by thiosulphate clearances gave results which did not differ

appreciably from those obtained by the cruder method of estimating the filtration rate. In Cases 5 and 6 and in Control 5 the bicarbonate absorptions per 100 ml. of glomerular filtrate, calculated from the urea clearances, were respectively 0·93, 0·85, and 1·60 mM before the phosphate infusions and 0·86, 1·09, and 1·51 mM after the phosphate infusions. These findings agree very

TABLE II

Relationship between the Reabsorption and Excretion of Bicarbonate and the Plasma Concentration of Bicarbonate

In each subject the two lines of data have the same significance as in the previous Table.

			Plasma				*Urine*				*Bicarbonate*		
Subject	*Glomerular filtration (ml./min.)*	*Urine flow (ml./min.)*	*$BHCO_3$ (mM/L.)*	*$p.CO_2$ (mm. Hg)*	*pH*	*Cl' (mM/L.)*	*$BHCO_3$ (mM/L.)*	*$p.CO_2$ (mm.Hg)*	*pH*	*Cl' (mM/L.)*	*Filtered (mM/min.)*	*Excreted (mM/min.)*	*Reabsorbed per 100 ml. filtrate (mM)*
Case 1	93	2·18	11·2	40	7·13	114	6·60	75	6·55	42·4	1·04	0·014	1·09
	122	4·13	12·2	25	7·30	117	0·65	42	5·80	12·7	1·47	0·003	1·22
Case 2	72	3·92	17·0	40	7·24	107	7·70	91	6·55	23·0	1·22	0·030	1·65
	124	3·96	18·3	33	7·37	105	0·50	85	5·25	7·7	2·27	0·002	1·83
Case 3	86	1·20	9·2	18	7·34	115	11·80	75	6·80	54·0	0·79	0·014	0·90
	132	2·65	13·3	27	7·38	112	0·12	32	5·24	8·5	1·75	0·000	1·33
Case 4	51	2·25	15·5	28	7·34	117	3·70	73	6·27	61·0	0·79	0·009	1·53
	84	6·45	16·7	22	7·50	111	0·55	43	5·76	8·5	1·42	0·004	1·67
Case 5	34	1·94	9·8	21	7·30	115	3·70	55	6·40	15·4	0·33	0·007	0·96
	30	2·70	8·6	20	7·25	115	0·09	15	5·13	25·6	0·26	0·000	0·86
Case 6	88	2·25	9·0	20	7·28	126	12·5	63	6·91	51·3	0·79	0·028	0·87
	92	3·35	10·9	26	7·24	122	0·14	30	5·09	37·6	1·00	0·000	1·09
Control 1	95	1·65	6·4	22	7·09	114	0·04	27	4·66	265·4	0·61	0·000	0·64
	115	4·60	11·7	27	7·25	106	0·04	29	4·80	3·5	1·35	0·000	1·17
Control 2	115	2·60	16·6	43	7·19	93	0·06	32	4·82	57·5	1·91	0·001	1·66
	85	2·90	17·8	26	7·43	85	0·05	25	4·36	12·8	1·51	0·001	1·78
Control 3	125	2·94	18·2	44	7·22	97	0·04	28	4·61	56·5	2·80	0·000	1·82
	132	4·18	21·8	29	7·50	88	0·04	34	4·60	18·8	3·36	0·000	2·18
Control 4	143	3·55	9·9	23	7·26	114	0·05	27	4·88	137·0	1·42	0·000	0·99
	133	4·23	9·4	22	7·26	111	0·04	28	4·74	32·5	1·25	0·000	0·94
Control 5	118	1·62	16·0	36	7·26	108	0·03	26	4·64	32·5	1·89	0·000	1·60
	186	2·28	15·1	26	7·38	108	0·01	21	4·41	6·8	2·81	0·000	1·51

closely with those shown in Table II, which were determined from the thiosulphate clearances.

In both Tables the glomerular filtration rates, volumes per minute, and all expressions of excretion and absorption have been corrected to a body-surface area of 1·73 sq. metres. This renders possible a comparison of the findings in the test and control groups, as well as a correlation with the results in normal adults published by Pitts and his fellow-workers. The original surface areas were determined from the nomogram showing the relationship of height and weight to surface area in childhood (Duncan, 1947).

Interpretation of results. It will be seen from Table I that after administration of phosphate there was no obvious difference in the output of free acid or

ammonia between the group of patients and that of the controls, but that before the administration of phosphate both these excretions were significantly lower

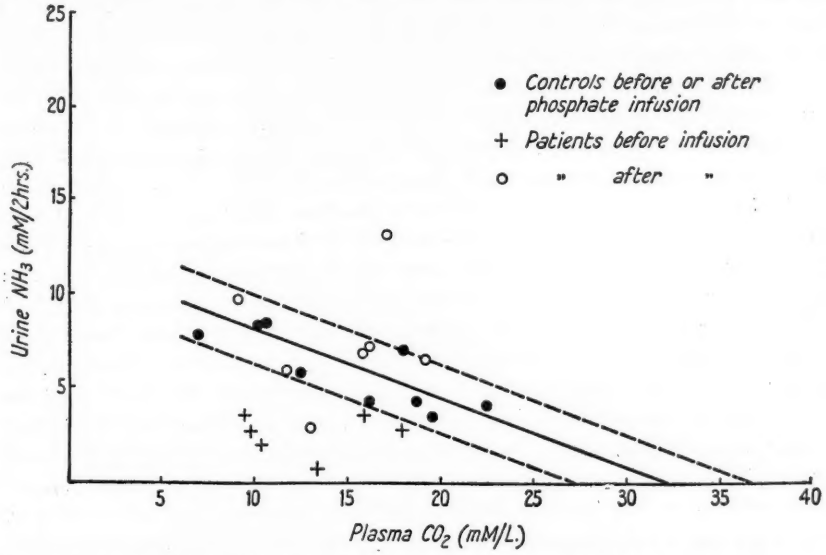

FIG. 1. The relationship between the urinary ammonia and the plasma carbon dioxide content.

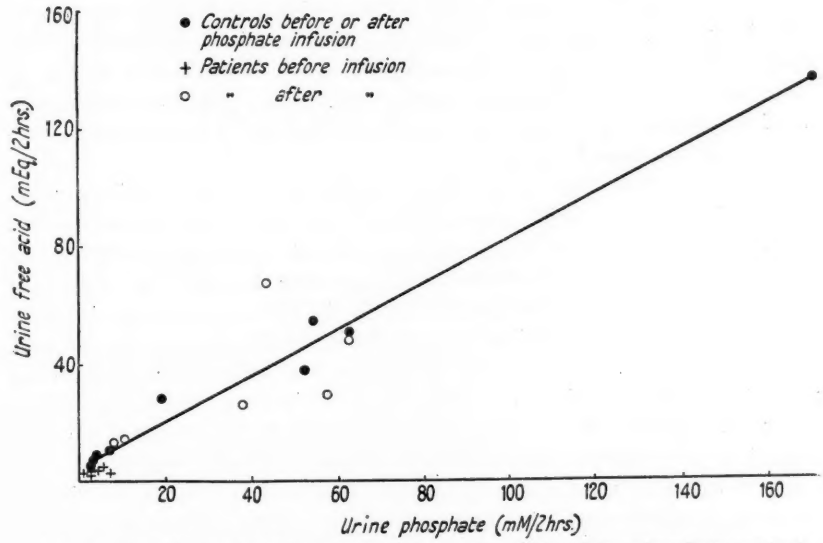

FIG. 2. The relationship between the urinary free acid and the phosphate content of the urine.

in the group of patients. These facts are perhaps better illustrated in Figs. 1 and 2. In the first figure, relating the urinary excretion of ammonia to the

plasma total carbon dioxide, the control values before and after phosphate have a roughly linear relationship. This is shown by the continuous straight line, the slope of which agrees quite well with that given by adults with undamaged kidneys (Peters and Van Slyke, 1946). In the patients, the values before phosphate administration fall below the normal area; after phosphate administration they tend to enter the normal area and the value in one case lies well above it. Similar findings are shown in Fig. 2, which relates urinary phosphate excretion to urinary free acid content. In the controls there is a linear relationship. This confirms other work (Schiess, Ayer, Lotspeich, and Pitts, 1948). Before phosphate, the values in the patients fall below the line. After phosphate they tend to be distributed about it. Reference to Table II shows that in the patients the concentration of bicarbonate in the urine before phosphate administration was significantly higher than in the controls. This confirms observations published by Stapleton (1949). After phosphate administration the urinary bicarbonate concentration in all the patients fell markedly, but in three it was still somewhat higher than in the control group. It will also be seen from the Table that the partial pressure of carbon dioxide in the urine is higher in the group of patients than in the controls; in fact, its value in each individual case is higher than in any control. After administration of phosphate the values in controls are essentially unaffected, but those in patients show a marked drop, and in five cases out of six become similar to those in the controls. This fall in the partial pressure of urinary carbon dioxide indicates a diminution in the absorption of sodium bicarbonate in the distal tubules, since it is this mechanism alone which gives rise to a partial pressure in the urine greater than that in the plasma (Pitts, Ayer, and Schiess, 1949). The urinary bicarbonate is also lowered, indicating an increased absorption of bicarbonate in the nephron as a whole. In view of the fall in distal tubular absorption, the inference is that the administration of phosphate has considerably increased the absorption of sodium bicarbonate in the proximal tubules.

This effect of phosphate on proximal tubular absorption is entirely unexpected, and this aspect of the results obtained will now be further elaborated. In Fig. 3 the absorption of bicarbonate per 100 ml. of glomerular filtrate has been related to the partial pressure of urinary carbon dioxide. The continuous line is reproduced from another publication (Pitts, Ayer, and Schiess, 1949), in which the various values obtained in normal adults fell in the area demarcated by the dotted lines. The shape of the continuous line indicates the fact that the proximal tubular mechanism is normally capable of dealing with about 2·2 mM of bicarbonate per 100 ml. of glomerular filtrate. This type of absorption has no effect on the urinary partial pressure of carbon dioxide, which therefore remains at the plasma value. Bicarbonate absorption above the level of 2·2 mM is carried out by the distal tubular mechanism. There is therefore a sudden increase in the urinary partial pressure of carbon dioxide, since the exchange of sodium ions for hydrogen ions gives rise to an increased concentration of carbonic acid in the urine. It is interesting to note that the control values before or after phosphate fall within the normal adult area. A few controls not shown

in Table II, and not rendered acidotic, have been included in the figure, in order better to demarcate the bend in the curve. Before phosphate administration, the points relating to the cases of hyperchloraemic acidosis are situated above and to the left of the normal area. This must mean that at absorption levels

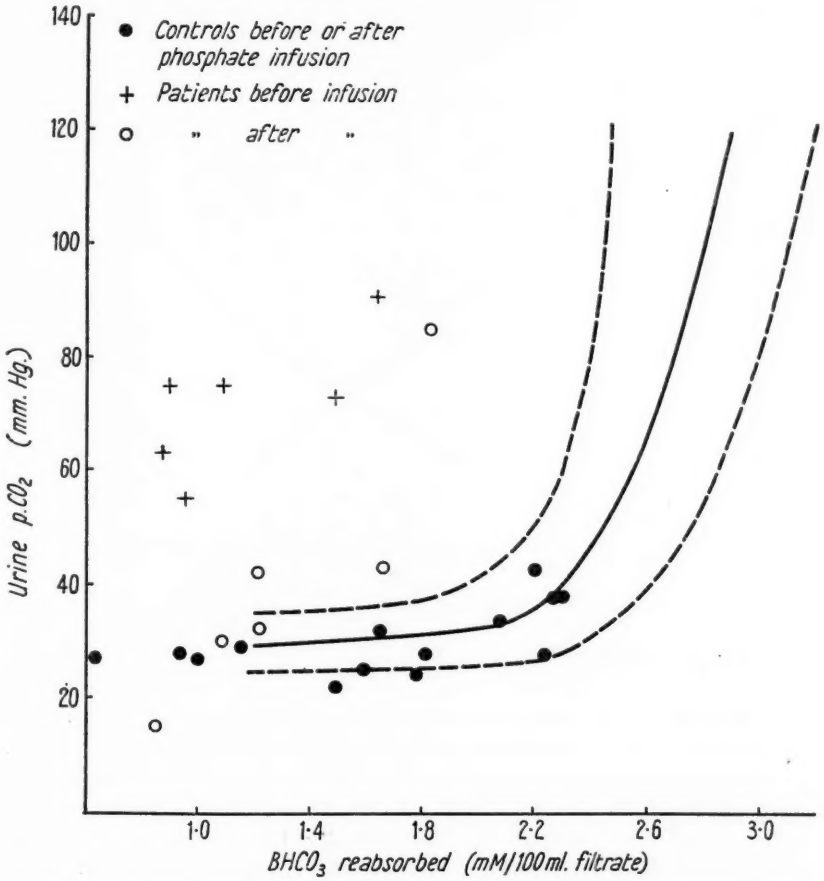

FIG. 3. The relationship between the partial pressure of urinary carbon dioxide and the total reabsorption of bicarbonate.

below 2·2 mM of bicarbonate per 100 ml. of glomerular filtrate the distal tubular mechanism has been brought into play. At these levels of absorption a normal proximal tubular mechanism would have dealt with all the bicarbonate, leaving little or none for absorption by the distal tubules. Here again we have an indication of faulty absorption in the proximal tubule. After phosphate administration, the abnormal values show a marked tendency to approach or enter the normal area. As the points tend to move down and to the right, this probably means increased absorption of bicarbonate by the proximal tubular mechanism.

Discussion

It is already apparent that the tubular mechanisms concerned in the production of free acid and ammonia are quite normal in nephrocalcinosis infantum. The fact that they have previously been regarded as inadequate is due to the

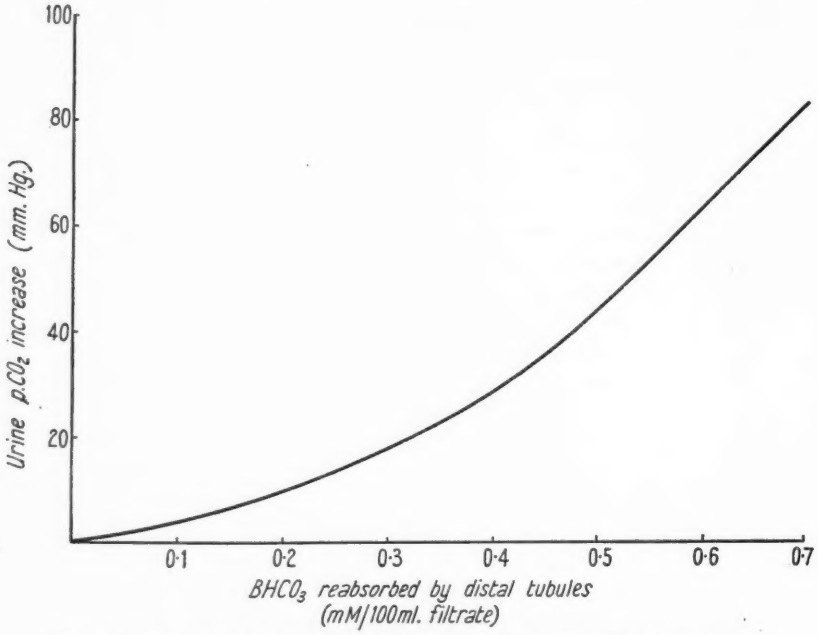

FIG. 4. The relationship between the increase of urinary p.CO_2 above that of plasma and the bicarbonate reabsorption in the distal tubules.

inhibitory action of an excess of bicarbonate within the distal tubules. This excess probably results from faulty absorption in the proximal tubular system. It is possible by consideration of Fig. 3 actually to determine the absorption of bicarbonate in the proximal tubules. From the smooth line points can be obtained which relate normal distal tubular absorption with the rise of the partial pressure of urinary carbon dioxide above that of the plasma. Since 2·2 mM of bicarbonate per 100 ml. glomerular filtrate are absorbed by the proximal tubule, it is only necessary to deduct this figure from total absorptions which exceed it in order to determine distal tubular absorptions at given urinary partial pressures of carbon dioxide. The rise of partial pressure above that of plasma is determined by subtracting from the urinary partial pressure the mean plasma value of 35 mm. Hg. In this way Fig. 4 has been constructed. Given the partial pressure of carbon dioxide in plasma and urine, it is now possible to determine distal tubular absorption. Since this absorption mechanism is identical with that of free acid production, there seems every reason to believe that it is normal in nephrocalcinosis infantum. The graph may therefore also be used in such cases. Having determined a distal tubular absorption in this way,

it is only necessary to deduct the figure so obtained from that of the total absorption in order to obtain the proximal tubular absorption. In this way Fig. 5 has been constructed from the values shown in Table II. The control cases both before and after phosphate give points which fall on a straight line.

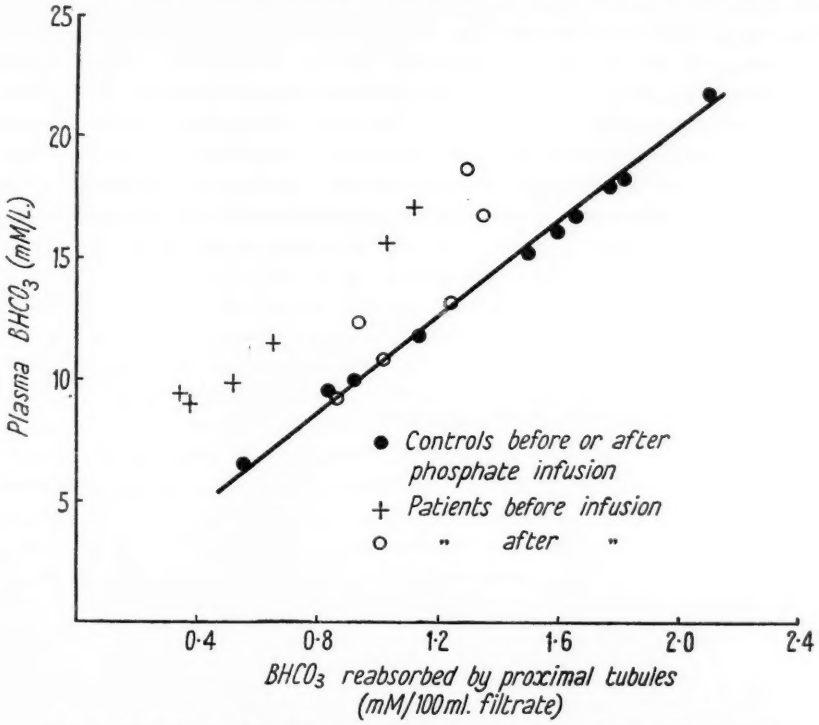

FIG. 5. The relationship between the plasma bicarbonate and the bicarbonate reabsorption in the proximal tubules.

This results, of course, from the fact that under conditions of acidosis there is more or less complete absorption of bicarbonate by the proximal tubules of the normal kidney (Pitts, Ayer, and Schiess, 1949). The points relating to the cases of nephrocalcinosis infantum before the administration of phosphate fall above this line. This directly indicates a faulty absorption of bicarbonate in the proximal tubules of these patients. It can also be seen from the figure that the administration of phosphate resulted in an increased proximal tubular absorption in five of the six cases. It is interesting to note that the three points still falling above and to the left of the line relate to the patients in whom the bicarbonate concentration in the urine remained above normal. This can now be explained by the facts that absorption was still not quite complete in the proximal tubules, and that in the distal tubules the high phosphate concentration, by a competitive mechanism, prevented absorption. The bicarbonate therefore found its way into the urine.

It would thus seem that in cases of idiopathic hyperchloraemic renal acidosis there is defective absorption of bicarbonate in the proximal tubules. Phosphate in high concentration in the glomerular filtrate helps to correct this fault. This may mean that phosphate is essential to the normal mechanism of absorption and that where this mechanism is faulty the phosphate concentration must be very much raised in order to produce normal absorption. Defective bicarbonate absorption in the proximal tubules may lead to an increased absorption of chloride. There seems to be a reciprocal relationship between the absorptions of these substances (Pitts, Ayer, and Schiess, 1949) which might account for the hyperchloraemia of the disease. Whatever the mechanism may be, the continued failure of bicarbonate absorption in the proximal tubules leads to the presence of bicarbonate in fairly high concentration in the distal tubules. This would not only cause increased loss of bicarbonate in the urine, but would inhibit the excretion of free acid and ammonia by the distal tubule (Sartorius, Roemmelt, and Pitts, 1949). In this way the conservation of base would be completely upset, and its failure would result in a continued acidosis and consequent hypercalcuria, owing to the mobilization of calcium to neutralize acid radicals. The resulting sequence of metabolic abnormalities would be as described by Albright, Burnett, Parson, Reifenstein, and Roos (1946). The calcification and other pathological changes noted in the distal convoluted and collecting tubules would readily result from the hypercalcuria and the continued state of chronic acidosis. The macroscopic and histological lesions seen in nephrocalcinosis infantum would thus be a result, not a cause, of the condition.

Although a detailed description of this disease would be out of place here, it is felt that certain points can be made from our clinical experience. In our hands treatment with alkalis, such as sodium citrate or a citrate-citric acid mixture, resulted in a notable clinical improvement, but contrary to most recorded findings (Greenspan, 1949; Albright, Burnett, Parson, Reifenstein, and Roos, 1946; Stapleton, 1949) a normal alkali reserve was not maintained by this treatment. Polyuria and thirst remained, though they seemed less severe. When the children were dehydrated, a few leucocytes per high-power field were found in the urine; the exact number was not determined. At other times they were very scanty. The finding of these cells suggested the need for investigating the chemical state of the blood and urine in infants thought to be suffering from urinary tract infection and pyuria. In this way additional cases of nephrocalcinosis were found and a biochemical diagnostic test was elaborated for the purpose. The test depended on the occurrence of a raised partial pressure of carbon dioxide in the urine in the presence of a lowered alkali reserve. The pressure was said to be raised when it was above 50 mm. of mercury.

Since in this disease a high proportion of the total bicarbonate absorption occurs in the distal tubules, it is possible to explain the reported ill effects of sulphonamide administration (Baines, Barclay, and Cooke, 1945; Peterman, 1945). Sulphonamide is known to inhibit carbonic anhydrase, which is an important factor in distal tubular absorption. This class of drugs would therefore lead to an increase in the already severe acidosis, and should be avoided.

It would be difficult to explain their rapid ill effect if the proximal tubular absorption of bicarbonate was near the normal minimal fraction of 2·2/2·8 of its total absorption. This fraction is derived from the facts that up to 2·2 mM bicarbonate per 100 ml. of glomerular filtrate is absorbed by the proximal tubule, and that bicarbonate normally appears in the urine when its concentration in the glomerular filtrate exceeds 2·8 mM per 100 ml. (Pitts, Ayer, and Schiess, 1949).

Finally it should be pointed out that in the control group free acid and ammonia production, as well as bicarbonate absorption in both proximal and distal tubules, compared very favourably with the published data for adults with normal kidneys, after appropriate correction for body-surface area. This can only mean that these mechanisms reach maturity at a remarkably early age, possibly within the first year of life.

APPENDIX

Case Histories

The age and measurements given in each instance relate to the day on which investigation by means of a phosphate infusion was carried out.

Case 1. Peter F., aged three years; weight 29 lb., height 35½ in. He was first seen at the age of two years because of thirst, polyuria, and failure to thrive, associated with intermittent attacks of severe constipation. These symptoms had been present for one year; progress had been normal during the first year of life. On examination he was a miserable, thin, dehydrated boy, with deep regular breathing and a scaphoid abdomen. Hard faecal masses were readily palpable. The first dentition was complete, but the teeth were hypoplastic. The blood-pressure was 90/60. His weight was 22½ lb., and height 32 in. The urine was alkaline to litmus, and its specific gravity varied between 1,002 and 1,010. A trace of albumin was present at first, but later specimens were clear. There was no glycosuria, and the amino-acid paper chromatogram was normal. Microscopy showed an occasional pus-cell and casts when the child's condition was at its worst. Two mid-stream specimens gave growths of *Bact. coli*, but subsequent cultures were sterile. A 24-hour specimen of urine had a volume of 2,000 ml. The plasma alkali reserve and chloride were respectively 16·6 and 134 mM per litre; the serum-sodium and serum-potassium were respectively 144 and 2·6 mEq per litre. The blood-urea on admission was 70 mg. per 100 ml., but subsequent specimens were normal. The urea clearance corrected for body size was 120 per cent. of the normal average. The serum contained 48 King-Armstrong units of alkaline phosphatase in each 100 ml. The serum-calcium, determined after two weeks on alkali treatment, was 11·1 mg. per 100 ml. Radiological investigation revealed bilateral renal calcification (Plate 27, Fig. 6). The long bones and epiphyses were normal.

This child was treated with a citrate-citric acid mixture in amounts containing nine gm. of sodium citrate daily for one year. He grew and was physically well most of the time, but polyuria and thirst were little changed, and there were days when he was very irritable and off colour. The plasma alkali reserve and chloride were within normal limits on two occasions only; usually there was

acidosis and hyperchloraemia. When he was re-admitted for further investigation at the age of three years, there was no change in the X-ray appearance of the kidneys. Treatment was stopped for ten days prior to the phosphate infusion.

Case 2. Frank F., aged 29 weeks; weight 12 lb., height 25 in. He was admitted to hospital at the age of 21 weeks suffering from frequent loose stools, as well as attacks of unconsciousness and stiffness lasting for about five minutes. He had made good progress till the age of 16 weeks, when he began to vomit after feeds, and became constipated. He was admitted to another hospital, and discharged after a fortnight. No definite diagnosis had been made. He continued vomiting, and became fretful and listless. At this stage the bowels were moving once a day.

On examination he was dehydrated, and his temperature was 106° F. After two critical days, with intravenous infusions and chemotherapy with penicillin and sulphamezathine, he made a good recovery. Ten days later, when he was vigorous and having normal stools, his plasma alkali reserve was only 11·5 mM per litre. In spite of this his urine remained faintly alkaline to litmus. Occasionally a trace of albumin was present, but there was no glycosuria, and an amino-acid paper chromatogram was normal. The specific gravity ranged from 1,004 to 1,010. Microscopic examination revealed an occasional pus-cell. The volume of a 24-hour specimen was 660 ml. on a daily fluid intake of 1,100 ml. The plasma-chloride was 124 mM per litre, and the blood-urea and plasma inorganic phosphorus were respectively 30 and 2·9 mg. per 100 ml. The plasma contained 5·1 King-Armstrong units of alkaline phosphatase in each 100 ml.

A week later there was a severe relapse of the diarrhoea, necessitating his re-admission. On this occasion there was a bilateral suppurative otitis media. As a result of further infusions and chemotherapy the diarrhoea was controlled, and his clinical condition improved. His plasma alkali reserve remained low and the plasma-chloride raised. The urine was alkaline. The phosphate infusion was carried out three weeks later.

Case 3. Tony R., aged 11 months; weight 19½ lb., height 27 in. He had two short spells in hospital at the age of eight months, because of attacks of extreme listlessness and pallor from which recovery was rapid. A dry mouth and excessive thirst were noted on one occasion. Progress had been normal until the age of seven months, when he began to refuse his feeds and suffered from vomiting and constipation.

He was again admitted because of an attack of collapse and pallor lasting a few hours. He was a well-nourished baby, and weighed 18 lb. The only demonstrable physical abnormality was a hard faecal mass in the left iliac fossa. The urine was alkaline to litmus, and contained a trace of albumin. There was no glycosuria, and an amino-acid chromatogram was normal. The specific gravity was 1,014. The plasma alkali reserve and chloride were respectively 15·5 and 117 mM per litre; the blood-urea and plasma inorganic phosphorus were respectively 47 and 1·66 mg. per 100 ml. The serum-potassium was 5·1 mEq per litre. He remained well for four days, and was discharged. The symptoms recurred, and he was re-admitted and again made a spontaneous recovery. On this occasion the biochemical findings were similar to those previously found. His weight had fluctuated between 17 and 18 lb. during the three months' period of observation. He was given sodium citrate in increasing amounts until he was taking 12 gm. daily. There was a gain in weight of 1½ lb. in a month, though the blood chemistry showed little alteration. Treatment was stopped for one week prior to phosphate infusion.

Case 4. Peter M., aged 26 weeks; weight 14 lb., height 26 in. He was admitted to hospital at the age of six months because of vomiting, refusal to take his feeds, and loss of condition. Progress had been normal until the age of four months. There was then failure to gain weight, which remained at 14 lb. for six weeks. During the next fortnight vomiting became frequent.

On examination he was a slightly sunken-eyed, irritable baby. His respirations were sighing. No other abnormality was demonstrated by physical examination. The urine was faintly acid to litmus; there was moderate albuminuria, but no glycosuria. Microscopic examination revealed one pus-cell in each four or five high-power fields, as well as infrequent clumps of pus-cells and casts. The plasma alkali reserve was 11 mM per litre, and the chloride and sodium were respectively 120 and 153 mEq per litre. The blood-urea, plasma inorganic phosphorus and serum-calcium were respectively 35, 2·9 and 10·2 mg. per 100 ml. The serum-potassium was 4·7 mEq per litre. X-ray examination of the kidney region revealed no abnormality. He fed eagerly, but became very constipated and more dehydrated. His breathing remained noticeably deep. He improved after treatment with streptomycin for 10 days, during which period his weight rose by ¾ lb. His plasma alkali reserve and chloride were now respectively 24 and 106 mM per litre. The urine remained faintly acid or neutral to litmus. The improvement was not maintained. Despite a second course of treatment with streptomycin the plasma biochemistry reverted to the picture seen on admission. At this stage the phosphate infusion was carried out.

Case 5. Maurice G., aged 1 year; weight 15 lb., height 27 in. He was admitted at the age of 10 months because of loss of weight, constipation, thirst, and irritability. There were in addition intermittent bouts of vomiting, each lasting three or four days. Symptoms began at the age of seven months, previous progress having been normal. On examination he was a wasted flabby child, weighing 14 lb. Physical examination revealed no other significant abnormality. The urine was alkaline to litmus, and there was neither albuminuria nor glycosuria. An occasional pus-cell was seen on microscopic examination. A 24-hour specimen had a volume of 600 ml. on a fluid intake of 1,050 ml.; the specific gravity was 1,004. A catheter specimen yielded a growth of *Bact. coli*. The plasma alkali reserve and chloride were respectively 14·3 and 127 mM per litre. The blood-urea, plasma inorganic phosphorus and serum-calcium were respectively 74, 4·2 and 11·0 mg. per 100 ml. The plasma alkaline phosphatase was 3·5 Jenner and Kay units per 100 ml. Subsequent blood-urea figures were 54, 52, and 36 mg. per 100 ml. Radiological examination of the kidney region did not reveal any calcification.

A course of streptomycin treatment was given for one week, and after a further fortnight the plasma alkali reserve was 18·9 mM per litre. Ten days later it had fallen to 15·9 mM per litre, and hyperchloraemia was demonstrated. A urine culture was sterile. Sodium citrate was then given for two weeks in daily amounts of 4 gm.; there was little change in the plasma alkali reserve or chloride. Treatment was stopped for five days before the phosphate infusion. During this period the child became febrile and dehydrated. In spite of the fact that 600 ml. of water had been given by mouth overnight, on the morning of the infusion there was some loss of skin elasticity. It was decided to proceed with the investigation, as the phosphate infusions in the previous cases had led to marked clinical improvement. The procedure was completed uneventfully, but the child died two hours later. Autopsy disclosed a well marked nephrocalcinosis and bilateral suppurative otitis media. After careful consideration of all the evidence in this case, and in view of our experience of the natural history

of the disease and of the effects of the experimental procedure, we are satisfied that death was due to the illness, and was not hastened by the infusion. In retrospect, however, we feel it was perhaps unwise to undertake the investigation at this stage of the illness.

Case 6. Robert L., aged 11 months; weight 16 lb., height 27 in. This child was first seen at the age of eight months. He had been irritable and difficult with his feeds, though thirsty and eager for water, and had lost two pounds of weight in two months. He was said to have been a cross baby from birth, but thrived normally until the age of six months. On examination he was a wasted and rather flabby baby, weighing 13½ lb. No other abnormality was demonstrated by physical examination. The urine was alkaline to litmus; a trace of albumin was present, but there was no glycosuria. Microscopic examination revealed an occasional pus-cell. Culture of a catheter specimen yielded a growth of *Bact. coli*. The plasma alkali reserve and chloride were respectively 15·1 and 113 mM per litre; the blood-urea and plasma inorganic phosphorus were respectively 31 and 3·5 mg. per 100 ml.

He was treated for five days with streptomycin, and three gm. of sodium citrate were given daily for two weeks in a citric acid-sodium citrate mixture. The plasma alkali reserve and chloride were now within normal limits, and the urine sterile. The citrate mixture was discontinued. Two months later the urine was still sterile on culture, but the plasma alkali reserve and chloride showed the same abnormalities as were seen before treatment. His weight had remained constant. The phosphate infusion was carried out 10 days later.

Selected controls

Control 1. Raymond F. (Arrested tuberculous meningitis). Age four years; weight 30 lb., height 35 in.

Control 2. Colin R. (Hydrocephalus). Age six months; weight 12 lb., height 24 in.

Control 3. Ivy C. (Arrested tuberculous meningitis). Age three years; weight 30 lb., height 38 in.

Control 4. Robert G. (Convalescent coeliac disease). Age 16 months; weight 22 lb., height 30 in.

Control 5. Robert F. (Convalescent herniotomy). Age 14 months; weight 20 lb., height 27 in.

We acknowledge with gratitude the help given by Professor J. C. Spence and Dr. G. Davison in the preparation of this paper, as well as the laboratory facilities made available to us by Dr. F. K. Herbert. Dr. E. B. Wright gave us access to her hospital beds, and her ward staff rendered most efficient assistance.

Summary

1. The primary fault in idiopathic hyperchloraemic renal acidosis appears to be faulty absorption of bicarbonate in the proximal tubules.

2. Bicarbonate absorption in the distal tubules, and the production of free acid and ammonia, are normal.

3. The presence of an increased concentration of bicarbonate in the urine of these infants is confirmed.

4. The raised partial pressure of urinary carbon dioxide in the presence of acidosis provides a useful diagnostic test, the application of which to a group of infants with so-called chronic pyuria revealed additional examples of idiopathic hyperchloraemic acidosis.

5. The renal mechanisms of bicarbonate absorption and of conservation of base normally reach maturity within the first year of life.

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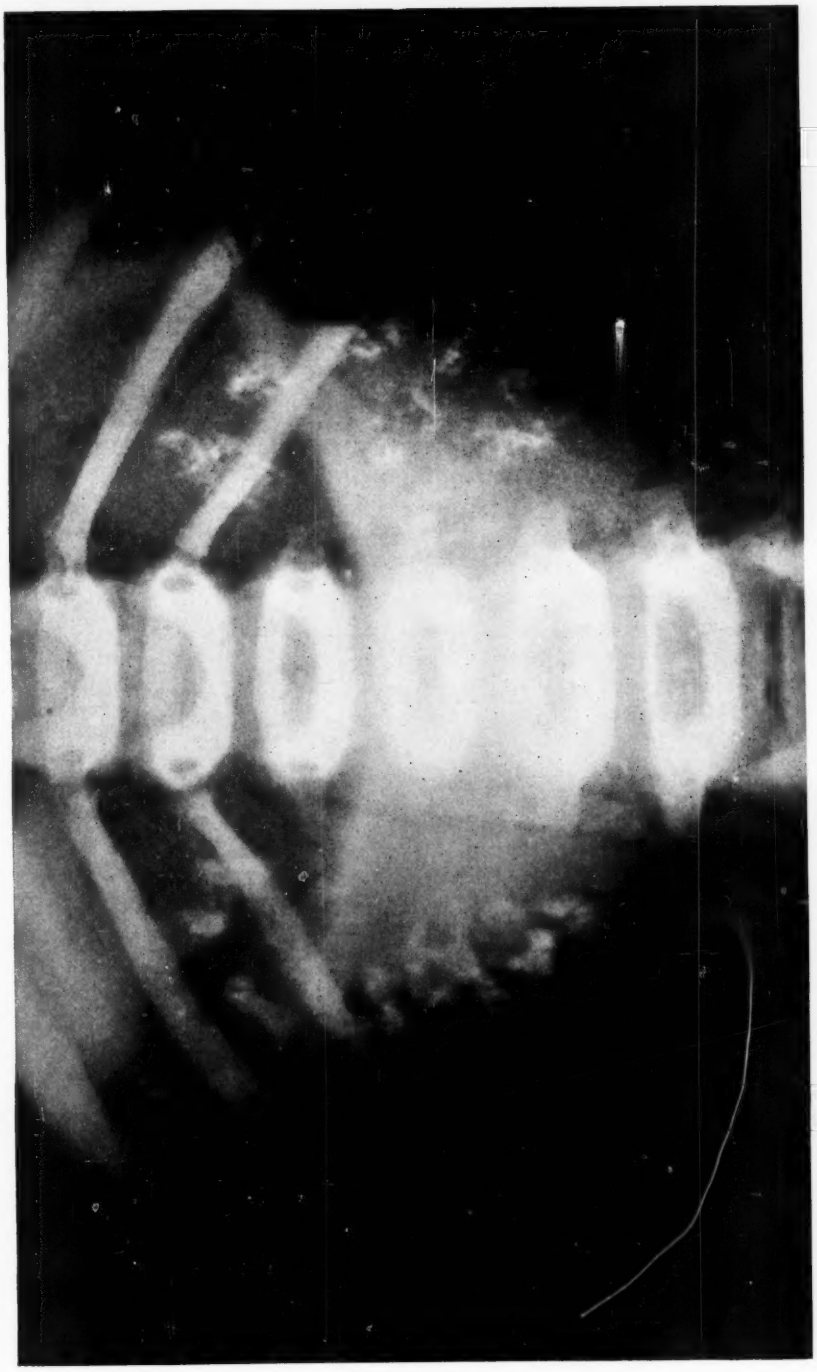

FIG. 6. Case I. X-ray showing bilateral renal calcification

616.74–009.125:616.4

DYSTROPHIA MYOTONICA: AN ENDOCRINE STUDY[1]

By J. E. CAUGHEY and J. BROWN

(From the Auckland Hospital, New Zealand)

With Plates 28 and 29

In the past three years in Auckland (population 275,000) we have had the opportunity to study dystrophia myotonica in 10 different families. Up to now these families have not been fully investigated, but we have examined 20 patients, 15 with the fully developed disorder, and five with cataract alone, thus obtaining support for the view expressed by Waring, Ravin, and Walker (1940) that the disorder is commoner than has been thought. Details of these families will be recorded elsewhere, but the main purpose of this paper is to report the results of an endocrinological investigation carried out on seven male and two female patients in whom the disorder was fully developed. In the past most of the study of this disease has been along purely clinical lines, recording its signs and symptoms and investigating its inheritance. Early studies of the ductless glands, according to Wilson (1940), showed changes which were too banal for any conclusions to be drawn. Adie and Greenfield (1923) described changes in the pituitary body and in the cortex of the suprarenal glands, which while not absolutely pathological 'were beyond what is usual'. Other endocrine glands were not described. There have been few clinical studies of endocrine function directed to correlating it with the pathological findings. Recently there have been isolated reports of newer methods of investigation, such as estimations of the excretion of follicle-stimulating hormone and of 17-ketosteroids. We were attracted to the study of the disease by a wealth of clinical material, and by the fundamental nature of the problem which it raises with its familial incidence and its variety of glandular dystrophies associated with a disorder of muscular function.

Case Reports

Family I (M.)

Case 1. Myopathy, myotonia, bilateral cataract, premature frontal baldness, hypogonadism, hypothyroidism, small pituitary fossa, and hyperostosis frontalis.

F. A. M., an unmarried man of 45 years, pensioned owing to disablement. At the age of about 27 years he had noticed wasting of his arms, legs, and neck muscles. This had progressed steadily and for the last three years he had been completely disabled, being unable to raise his head or to stand alone. Five

[1] Received January 21, 1950.

years after the onset of muscle wasting he found difficulty in relaxing his grasp, and about the same time his vision began to fail owing to the development of bilateral lenticular opacities. Cataracts were successfully treated five years later. Seven years after the onset he had to give up farming on account of increasing weakness. Frontal baldness had developed in his early twenties. He first shaved at the age of 17 years, and since then had not had to shave more than every third day. The hair on his body had become soft and scanty during the past 10 years. Sexual power and libido had deteriorated, but he still had some potency and occasional nocturnal emissions. He had complained of the cold in recent years. His parents and grandparents were healthy. One brother, S. M., aged 41 years, had bilateral lenticular opacities, but no other evidence of the disease. Another brother and a sister were normal. An aunt on the maternal side had cataracts, but was not examined by us.

On physical examination he was a tall, middle-aged man with frontal baldness, a myopathic facies, and scanty eyebrows, body-hair, and beard. His measurements were: height, 5 ft. 10 in.; span, 5 ft. 10 in.; vertex to symphysis pubis, 2 ft. 11 in.; symphysis pubis to sole, 2 ft. 11 in. The facial hair was soft and scanty on the chin and moustache area. The pubic hair was of female distribution, the axillary hair was normal, and there was no hair on the legs. The skin of his fingers was shiny and dystrophic in appearance. He was unable to sit without assistance, and required assistance when walking. His visual acuity was reduced, as a cataract had been removed from each eye. The facial muscles were wasted and very weak, and there was almost complete atrophy of both sternomastoid muscles. There was great wasting and weakness of all muscles of the forearms. The abdominal muscles were weak, and the lower limbs were wasted and weak in all movements. His gait when assisted was unsteady and of a 'slapping' and 'steppage' type. When he was seen about 12 years before, there had been myotonia of the grasp but, probably owing to excessive weakness, this was now slight. There was slight mechanical myotonia in the tongue and the thenar and hypothenar eminences. All the deep reflexes were lost. Sensory appreciation was normal. The testes were soft and very small. His mental state was good. He was co-operative and not subject to any variations in mood. The cardiovascular system was normal, with a blood-pressure of 150/75. Other systems were normal.

Investigations. The blood count was normal and the Kahn reaction negative. The cerebrospinal fluid was normal. The basal metabolic rate was —48 per cent. and —34 per cent. The serum-cholesterol was 360 mg. per 100 ml., the total non-protein nitrogen 33 mg. per 100 ml., the serum-chlorides 556 mg. per 100 ml. (as NaCl), the serum-calcium 10·7, 10·5, and 9·1 mg. per 100 ml., serum-phosphorus 4 and 3·3 mg., serum-sodium 327 mg., and serum-potassium 17 mg. per 100 ml. The serum acid phosphatase was 1·2 units, and alkaline phosphatase 22 King-Armstrong units. Tests of glucose tolerance and insulin tolerance in 1947 and 1949 showed a delayed return of the blood-sugar to a normal level after 50 gm. glucose, and a delayed fall in the blood-sugar level after insulin (Tables III and IV). The excretion of follicle-stimulating hormone was positive to 96 mouse units. The potassium-resistance test for adrenal cortical function (Cutler, Power, and Wilder, 1938) gave an equivocal result. The 17-ketosteroid excretion was 1·3 and 1 mg. per 100 ml. in 24 hours. The electrocardiogram showed elevation of the ST segment in leads I and II, and slight ventricular myocardial damage seemed probable (Dr. E. Roche). Radiologically the lung fields were clear and the heart shadow normal. An X-ray of the skull (Plate 28, Fig. 1) showed the vault to be normal in shape, and the calvarium thickened, with hyperostosis interna frontalis et parietalis; the sinuses were within normal

limits, the mandible normal, and the sella turcica small, with a pneumatized dorsum sellae. The pineal body was calcified.

Family II (H.)

Members of two families with the same father were investigated. The father was examined by us, and had a bilateral posterior polar cataract, but no other signs of dystrophia myotonica. By his first wife he had a son (R. F. H., Case 2), and a daughter whom we did not examine. By his second wife he had three sons and a daughter, all of whom had the complete picture of the disorder. Two of them (D. G. H., Case 3, and P.H., Case 4) are described.

Case 2. Myopathy, myotonia, bilateral cataract, frontal baldness, hypogonadism, and small pituitary fossa.

R. F. H. was a retired farmer, aged 42 years. In 1941 he had become aware of difficulty in relaxing his grasp, soon followed by weakness and wasting in his forearms, legs, and neck muscles. The wasting and weakness had progressed and the myotonia had persisted. For four years there had been impairment of sexual power and libido, with complete loss of potency in the last six months. Frontal baldness began in his early twenties. He had lately become irritable and less reliable.

Physical examination showed a well-developed man, with frontal baldness and a myopathic facies. He had extensive body-hair and normal facial hair. There was general wasting of his facial, temporal, and sternomastoid muscles, the latter giving a rounded swan-like appearance to the neck. The deltoid muscles were hypertrophied but weak, and there was severe wasting and weakness of the forearms and upper arms, the small muscles of the hands being unaffected. There was great wasting of the legs, and to a lesser extent of the thighs. All the deep reflexes were much impaired. The grasp was myotonic on both sides, and myotonia of the tongue, thenar, hypothenar, and calf muscles was present on percussion. Visual acuity was 6/12 in both eyes owing to lenticular opacities. The testes were small and soft. The cardiovascular system was normal.

Investigations. The blood Kahn test was negative, and a blood count was normal. The serum-calcium was 10·7 mg., serum-phosphorus 3·6 mg., and serum-cholesterol 180 mg. per 100 ml. The cerebrospinal fluid was normal, the basal metabolic rate was —12 per cent. and —8 per cent. The electrocardiogram was normal. The glucose-tolerance and insulin-tolerance tests gave normal results (Tables III and IV). The excretion of 17-ketosteroid on two estimations was 2·5 and 4·5 mg. in 24 hours. A radiograph of the chest was normal. An X-ray of the skull showed a normal vault, large frontal sinuses, and a normal sella turcica. The mandible and the pineal body were not seen.

Case 3. Myotonia, myopathy, auricular flutter.

D. G. H., an unmarried panel-beater, aged 26 years. In 1945 he developed palpitation and breathlessness and was admitted to hospital, where auricular flutter was diagnosed. For two years previously he had noticed difficulty in relaxing his grasp, and weakness of his wrists and legs. Frontal baldness began to develop at 21 years of age. The sexual functions were unimpaired.

On physical examination he was a slightly built man, with frontal baldness. His body-hair and secondary sexual hair were normal. His facies was

myopathic, and his neck rounded and swan-like owing to wasting of the sternomastoid muscles. The forearms were wasted, and the extensors of the wrists weak. The deep reflexes of the arms were absent; the knee-jerks were reduced. There was myotonia of the grasp and myotonia on percussion of the tongue, thenar and hypothenar eminences, and calves. The testes were normal. The visual acuity was normal, and there were no lenticular opacities. The pulse-rate was 110 per minute, the rhythm regular, and the vessels soft. The apex beat was in the fifth space three inches from the mid-line. The heart sounds were normal, and there were no murmurs. The blood-pressure was 115/85. An electrocardiogram showed an irregular rhythm with a 4 : 1 to 7 : 1 flutter. The ST segment was normal.

Investigations. The blood count was normal, and the Kahn reaction negative. The serum-calcium was 10·4 mg., serum-phosphorus 3·2 mg., and serum-cholesterol 210 mg. per 100 ml. The basal metabolic rate was +38 per cent. and +27 per cent. The serum acid phosphatase was 2 units. Glucose tolerance (Table III) and insulin tolerance were normal. The excretion of 17-ketosteroid on two estimations was 4·2 and 5·5 mg. in 24 hours. A radiograph of the chest was normal. A skull X-ray showed a vault of normal shape; the bones were thickened, especially in the posterior parietal region. There was parietal hyperostosis interna, extending to the frontal region. The frontal sinuses were deep and the sella turcica normal. The mandible and the pineal body were not seen.

Case 4. Myotonia, muscular dystrophy, bilateral cataract.

P. H., *née* P. H., was a married woman, aged 33 years. Twelve years previously she had noticed a difficulty in relaxing her grasp, and six or seven years later a weakness and wasting of her right leg. Soon afterwards the weakness and wasting had become apparent in the left leg, upper limbs, neck, and face. Next she found difficulty in holding her back straight and, at times, a tendency to overbalance. For three years she had noticed deterioration of her vision, and 18 months ago the vision in her right eye had failed completely, and a cataract was excised. The left eye subsequently failed and a cataract was removed. She had had three children. The first had a cleft palate, and died of meningitis. The second had a cleft palate and hare-lip, and the third child was alive and well.

Physical examination showed a myopathic facies, with wasting of all the facial muscles; the neck was swan-like owing to complete wasting of the sternomastoids. There was wasting of the forearms with weakness, which was more marked in the dorsiflexors of the wrists. The muscles of the legs were wasted, and the dorsiflexors of the feet weak. The grip was myotonic and there was myotonia on percussion of the tongue, thenar and hypothenar eminences. All the deep reflexes of the lower limbs were absent. Before her operation for cataract there were bilateral lenticular opacities; on slit-lamp examination these were punctate or small and scale-like, some of those situated under the cortex being bluish-green. Outside the nucleus they had gradually increased so that both lenses were opaque (Mr. W. A. Fairclough). An X-ray of the skull showed a normal-shaped vault; the calvarium was thickened throughout, with marked hyperostosis frontalis interna and hyperostosis parietalis, somewhat resembling that seen in Paget's disease. The sinuses were within normal limits, with pneumatization of the dorsum sellae. The sella turcica was within normal limits. The pineal body was calcified. Laboratory investigations were incomplete. The 17-ketosteroid excretion was 2·3 mg. in 24 hours.

Family III (K.)

Case 5. Myotonia, myopathy, cataract, frontal baldness.

E. L. K., a returned soldier, aged 32 years. While a prisoner of war in Germany in 1944 he had noticed difficulty in relaxing his grip, soon followed by wasting and weakness of the right shoulder muscles. The wasting went on to involve the muscles of his face, neck, forearms, shoulder girdles, and legs. His vision had recently deteriorated. There had been no impairment of sexual power or libido.

Physical examination showed extensive frontal baldness and a myopathic facies, with early wasting of the facial muscles. The sternomastoid muscles were completely wasted, and there was great wasting of the left deltoid and pectorales, and of the spinati and trapezii. The lower limbs were normal. There was myotonia of the grip and myotonia on percussion of the tongue, the thenar and hypothenar eminences, the deltoids, and the flexors of the forearms. The knee-jerks were diminished and the right ankle-jerk absent. Visual acuity was unimpaired, but both eyes showed early cataract, with a few striae radiating from the posterior pole of the right lens and a few minute opacities in the left lens. The slit-lamp revealed multiple punctate opacities of various sizes in the anterior cortex of both lenses, more marked at the equator. A few of the opacities were greenish in colour.

Investigations. A blood count was normal, and the blood Wasserman reaction negative. The cerebrospinal fluid was normal. The serum-calcium was 10·8 mg. per 100 ml., and serum-cholesterol 180 mg. per 100 ml. 17-ketosteroid excretion was 4·8 mg. in 24 hours. Insulin sensitivity was normal (Table IV). Biopsy from the left deltoid muscle showed irregular changes in the muscle-fibres, some of which were hypertrophic and many wasted, and an increase of fibrous tissue. There was loss of the transverse striations and multiplication of the nuclei.

Family IV (W.)

Case 6. Complete picture of dystrophia myotonica: myotonia, wasting, cataracts, failure of sexual power and libido, left bundle-branch block.

C. C. W., a carpenter, aged 41 years. When 34 years of age he noticed failure of sexual power, which went on to complete loss of potency and libido. Four years later his grasp became difficult to relax, there was weakness of his arms and legs and difficulty in swallowing, and his speech became slurred.

On physical examination he was a bald, wasted man with a myopathic facies. His speech was somewhat slurred and thick. The sternomastoid muscles were completely wasted. There was great wasting and weakness of all four limbs and of the abdominal muscles. Voluntary myotonia affected the grasp of both hands, and there was myotonia on percussion. All the deep reflexes were absent. Secondary sexual hair was scanty. The testes were small and soft, and the prostate gland very small. Visual acuity was normal. Slit-lamp examination revealed multiple punctate subcapsular opacities, longer and more numerous at the periphery. A few were green. There were posterior cortical radial opacities in both lenses. The pulse was slow and regular. The heart was not enlarged, and there was reduplication of the second sound at the apex. The blood-pressure was 100/55.

Investigations. A blood count was normal, and a blood Kahn test was negative. The cerebrospinal fluid was normal. The 17-ketosteroid excretion was 1·7 mg. in 24 hours, and a gastric test meal showed a low total acidity. Electro-

cardiography showed the heart-rate to be 50 per minute. The P waves were of low voltage, the PR interval 0·26 seconds, the QRS complexes widened, and the ST segment depressed in leads I and II and elevated in lead V_4. T was biphasic in leads I and II, and high in lead V_4. These findings suggested an impaired function of the sino-auricular node and myocardial damage affecting bundle-conduction, with a block of the left bundle-branch. An electrocardiogram taken two weeks later revealed no change. A radiograph of the chest was normal. A skull X-ray showed a normal vault with well-marked venous lacunae; the frontal and sphenoid sinuses were extensive and deep, the latter extending into the posterior clinoid processes. The mandible was elongated. The sella turcica was possibly small, but showed no calcification within; the dorsum sellae was completely pneumatized. The pineal body was not seen.

Family V (B.)

Case 7. Myopathy, myotonia, bilateral cataract, small pituitary fossa, and hyperostosis frontalis.

E. B., a married woman, aged 51 years, had noticed weakness of her neck muscles since the age of 30. In the past five years there had been progressive wasting and weakness of her forearms and legs, so that she had been bedridden for a year. At times she had noticed some difficulty in relaxing her grasp, but this was not troublesome. Her vision had not failed noticeably, but there had been loss of libido for several years. She had two sons, the younger, aged 28 years, having the fully developed disease (J. B., Case 8). The elder son was well. There was no history of cataract in the family.

Physical examination showed a middle-aged woman with grey hair, no baldness, and a myopathic facies. Her speech was slurred in character. Her body-hair and eyebrows were somewhat scanty, but of normal female distribution. The skin was soft and of fine texture. There was some wasting of the facial muscles. The sternomastoid muscles were almost completely atrophied, and were powerless. There was great weakness and wasting of the forearms and legs. Myotonia was slight. All the deep reflexes were reduced, and the ankle-jerks absent. There were bilateral posterior polar cataracts. Her mental condition was normal, and she was of average intelligence. The cardiovascular system was normal.

Investigations. The serum-calcium was 10·3 mg. and serum-phosphorus 4 mg. per 100 ml. The serum-sodium was 335 mg., serum-chlorides 556 mg. (as NaCl), and serum-cholesterol 310 mg. per 100 ml. A glucose-tolerance test showed a delay in the return of the blood-sugar to a normal level. Insulin sensitivity was normal (Tables III and IV). The excretion of follicle-stimulating hormone was strongly positive to 96 mouse units. The 17-ketosteroid excretion was 1·8 mg. in 24 hours. The water excretion test for adrenal cortical function (Robinson, Power, and Kepler, 1941) was suggestive of impaired function. The volume of the night urine was 435 ml., and that of the largest day specimen 315 ml., giving an index of 38. The basal metabolic rate was —4 per cent. An electrocardiogram showed low voltages throughout, a left bundle-branch block, and probably a first degree of heart-block. An X-ray of the chest was normal. A skull X-ray (Plate 28, Fig. 2) showed the vault to be normal in shape, but possibly enlarged owing to a thickening of all the membranous bones; there was extensive hyperostosis frontalis interna. The thickening was somewhat patchy, resembling that seen in Paget's disease. The sinuses and mandible were normal. The sella turcica was small, with calcification near the floor; there was no pneumatization of the dorsum sellae. The pineal body was not seen.

Case 8. Myopathy, myotonia, cataract, hypogonadism, mental retardation, small pituitary fossa, and hyperostosis frontalis.

J. B., a pensioner, aged 28 years, E. B.'s younger son. At school he was backward, but did not require special schooling. On leaving school at 13 years he was unable to take up any regular employment. At 17 he noticed a difficulty in relaxing his grasp, soon followed by weakness and clumsiness of his arms, legs, and neck muscles. The weakness and wasting progressed slowly. For two years prior to our examination his vision had been deteriorating.

On physical examination he was a dark, swarthy man of inferior intelligence. His facies was myopathic, with a slow lingering smile. There was early recession of the hair in the frontal region, but his body-hair was normal and of male distribution. His speech was slurred and indistinct. There was wasting of the sternomastoid muscles and of the muscles of the forearms and legs. There was marked myotonia of the grasp and, on percussion, of the tongue and small muscles of the hands. The knee- and ankle-jerks were absent. There was bilateral polar cataract. The testes were small and soft, but had normal sensation. The scrotum and penis were of normal size. The body-dimensions were: span 65½ in., height 65½ in., vertex to pubis 33 in., pubis to soles 32½ in.

Investigations. The serum-sodium was 332 mg. and serum-potassium 17·5 mg. per 100 ml.; the serum-cholesterol 200 mg., serum-calcium 9·9 mg., and serum-phosphorus 2·0 mg. per 100 ml. The basal metabolic rate was +9 per cent. Glucose tolerance and insulin sensitivity (Tables III and IV), and the clinical response of the patient to insulin, were normal. 17-ketosteroid excretion was 1·2 mg. in 24 hours. The water excretion test (Robinson, Power, and Kepler, 1941) produced 300 ml. of night urine, and the greatest hourly volume of day urine after fluid was 210 ml., giving an index of 35. The excretion of follicle-stimulating hormone was positive to 96 mouse units. An electrocardiogram showed a PR interval of 0·17 seconds, and a very small R wave in leads V_2 and V_3, with the probability of myocardial damage (Dr. E. G. Sayers). A skull X-ray (Plate 28, Fig. 3) showed the vault to be normal in size; all the membranous bones were thickened, with extensive hyperostosis frontalis interna and hyperostosis parietalis interna. The sclerosis was patchy, to some extent resembling Paget's disease. The sinuses were extensive and deep. The sella turcica was small, and the dorsum sellae thick and partly pneumatized. The pineal body was possibly calcified. His intelligence quotient by Wechsler's performance test was 74.

Family VI (S.)

Case 9. Myopathy, myotonia, hypogonadism, mental retardation, and small pituitary fossa.

F. S., a grocer, aged 33 years. He had always been a frail individual and afraid of other boys. At school he was backward. His occupational history was unsatisfactory, and for the last year he had been unemployed. He had first noticed difficulty in relaxing his grasp when 13 years of age. At the age of 15 he had noticed that his arm and leg muscles were becoming weaker and were wasting. The difficulty with his grip had become increasingly great. He had begun shaving at 21 years, and at 33 shaved every third day. His vision had not deteriorated. He felt the cold very much. Neither of his parents, to his knowledge, had any wasting, muscle disability, or cataract. A paternal cousin had wasting of his arms and legs. A brother and sister of the patient were reported to be well.

On physical examination he was a thin, swarthy man with a disinterested look, and below the average in intelligence. The head hair was dark, very fine and scanty, and the eyebrows were scanty. The facial hair was scanty and confined to the moustache and chin areas. The axillary and pubic hair were also scanty, the latter being of female distribution. The hair on his legs was fine but of normal distribution. His skin was dry and atrophic, with numerous melanomata. The thyroid gland was not palpable. There was marked myotonia of the grip, and myotonia of the tongue and thenar eminences on percussion. The facies was myopathic, and there was wasting of the sternomastoids and, to a lesser degree, of the limb muscles. The deep reflexes were normal. No cataracts were present. The prostate gland was very small. The cardiovascular system was normal.

Investigations. The blood Kahn test was negative. The serum-sodium was 340 mg., serum-potassium 16 mg., and serum-chloride 580 mg. per 100 ml.; the serum-cholesterol was 280 mg. and the serum-calcium 10·1 mg. per 100 ml. Glucose tolerance and insulin sensitivity (Tables III and IV), and the clinical reaction to insulin, were normal. 17-ketosteroid excretion was 3·1 mg. in 24 hours. The water excretion test (Robinson, Power, and Kepler, 1941) produced 360 ml. of night urine, and the greatest hourly day urine after fluid was 270 ml., giving an index of 31. Excretion of follicle-stimulating hormone was positive to 96 mouse units. An electrocardiogram showed some slurring of R in leads I and II, probably representative of myocardial damage. An X-ray of the skull (Plate 28, Fig. 4) showed a small, globoid and microcephalic vault. The bones were thick but of normal density, with marked venous lacunae. The sinuses were extensive and deep, especially the sphenoids, which extended into the posterior clinoid processes. The mandible was elongated. The sella turcica was very small, but showed no calcification within. The dorsum sellae was pneumatized. The pineal body was not seen.

Results of Endocrine Studies

Body growth. The skeletal proportions of these patients were within normal limits, the height and span being approximately equal, and the vertex-to-pubis about the same as the pubis-to-heel measurement. There was no radiological evidence of delay of the epiphyseal closures. These clinical observations, the previous history of the patients, and the endocrine studies to be discussed later leave little doubt that their hypogonadism began after puberty.

Hair growth. This will be discussed here, although secondary sex hair is considered by some workers (Albright, Smith, and Fraser, 1942) to be controlled by the adrenal glands. The frontal recession of head hair is often premature in dystrophia myotonica, occurring in the second or early in the third decade. In the present series it was apparent in all the male patients who had the disorder. The changes in body-hair were variable. Two male patients noted the scanty growth of their facial hair, which was restricted to the chin and moustache areas, and they did not have to shave until they were respectively 17 and 21 years old. In these two patients the evidence of hypogonadism appeared several years later. In four male patients the secondary sex hair was normal, and one had a heavy growth of hair on limbs, axillae, and chest. Two male sufferers from the disease shaved every third day; their axillary hair was fine, but of normal distribution; they had no chest hair, the pubic hair was of female

distribution, and in one of them the hair on the legs, which had been normal, was fine and reduced, while in the other it was absent. The eyebrows were thin in the outer third. In these two patients the basal metabolic rate was low, and there was other evidence of myxoedema; it therefore seemed likely that the recession of body-hair and eyebrows was due to the hypothyroidism.

Radiography of the Skull. Radiological changes in the skull were striking, and it is surprising that little emphasis has been laid on these changes by others. Scharnke and Full (1920) described a large frontal sinus in the presence of a normal sella turcica. Rouquès (1931) reported large frontal sinuses in two patients, and in four he found changes in the sella turcica. In two of our patients the sella was very small, and in the other four the sellae were bridged by an area of calcification. Fagin (1946) reported one patient with hyperostosis frontalis. In our patients we were impressed by the notable changes in the sella, the calvarium, and the sinuses, and we regard the high incidence of hyperostosis interna that we have encountered as being significant. The findings in nine patients may be enumerated as follows:

Enlargement of the sinuses	5
Thickening of the bones of the calvarium	6
Hyperostosis frontalis	5
Pneumatization of the dorsum sellae	5
Small sella turcica	5
Elongation of the mandible	3
Increased density of bone	5
Prominent venous lacunae	2
Calcification within the sella turcica	1

These findings are at first perplexing: on the one hand, the enlarged frontal sinuses suggest an overactivity of the anterior lobe of the pituitary and, on the other hand, the pituitary fossa is often quite small. This smallness of the fossa may mean that pituitary overactivity took place in the early years, and was later followed by partial atrophy and subsequent failure of the sella to enlarge. Two children, aged 6 and 3 years, of a dystrophic mother with a marked hyperostosis, had normal skull X-rays. J. B., the son of the dystrophic Mrs. E. B., showed hyperostosis frontalis similar to that seen in the mother. The frequency of the above radiological findings in dystrophia myotonica suggests a close relationship with the other factors of the disease. Schneeberg, Woolhandler, and Levine (1947), however, in an analysis of 700 cases of hyperostosis frontalis, were unable to show any relationship between thickening of the skull and the clinical state which accompanied it.

Gonadal function. In all the patients of the present series the onset of hypogonadism occurred some time after puberty, as is evident from the normal skeletal proportions, the normal development of secondary sex hair, the size of the genitalia, the normal voice, and the normal radiological appearance of the long bones and sinuses. Hypogonadism always began some time after the onset of myotonia and wasting. One female patient had noticed difficulty in relaxing her grip 12 years before, but had since given birth to three children.

In the male patients the size of the penis was normal and the scrotum was well developed; the distribution of pubic hair was normal except in two, in whom it was of female distribution. The testes in five were soft, and the size of a small almond; in two they were normal. Normal testicular sensation was present. Two male patients with advanced disease said that their libido was still normal. Sexual power was much reduced, but still present, and occasional emissions occurred. The prostate was examined in four, and was small in each case. Examination of the semen of one male patient failed to reveal active sperms. Testicular biopsy was carried out in three patients in an advanced stage of the disease, with the following results. *Case 1*, F. A. M. (Plate 29, Fig. 5): Atrophy both of seminiferous and of interstitial elements was almost complete in both testes. The basement-membranes of the seminiferous tubules persisted, but no spermatogenic or supporting cells were to be seen. A few vestigial Leydig cells were present. *Case 8*, J. B. (Plate 29, Fig. 6): In the specimen examined the seminiferous tubules had for the most part atrophied completely, the zones normally occupied by epithelial cells being filled by hyaline fibrous tissue. One or two tubules still contained spermatocytes with pyknotic nuclei, but there was no evidence of spermatogenesis. Interstitial cells were identified with difficulty and appeared degenerate. *Case 9*, F. S.: Two pale-grey portions of tissue of irregular contour were examined and found to consist of epididymal tubules and ducti efferentes. No spermatozoa were found in their lumens.

Gynaecomastia. Gynaecomastia was noted in one male patient only (F. A. M.), and followed treatment with testosterone, by injection and implant, for 12 months. The development of gynaecomastia in a proportion of eunuchoid males treated with testosterone was reported by McCullagh and Rossmiller (1941). Klinefelter, Reifenstein, and Albright (1942) pointed out that the production of this kind of gynaecomastia depends on the presence of androgen and the absence of spermatogenesis, conditions which were both present in this patient. Two other male patients were treated with testosterone but did not develop gynaecomastia.

Follicle-stimulating hormone. The assay of follicle-stimulating hormone in urine is at present the only direct method readily available of estimating a pituitary hormone. The test finds its greatest use in determining the cause of hypogonadism, since increased amounts are excreted in primary gonadal failure, and decreased amounts when the failure is secondary to pituitary insufficiency. We carried out the assay by the method of Klinefelter, Albright, and Griswold (1943), using the enlargement of the immature mouse uterus as the end-point. A result was considered positive when the mouse uterus weighed 10 mg. or more. Normal excretions by this method lie between 13 and 54 mouse units in 24 hours. Assays of follicle-stimulating hormone were carried out on five of our patients, four male and one female. Three of the male patients, F. A. M., J. B., and F. S., had the fully developed syndrome with gonadal atrophy, and their urine excreted in 24 hours was positive to 96 and negative to 192 mouse units. The excretion in the case of E. B., who was past the menopause, would normally be expected to have a high hormone value, and was strongly

positive to 96 mouse units. D. G. H., who had no loss of libido or sexual power, and whose testicles and prostate gland appeared normal, excreted normal amounts of the hormone (positive to 26 mouse units in 24 hours, and negative to 54). These results agree with those of Benda and Bixby (1947) who found in one of their patients an excretion of follicle-stimulating hormone positive to 96 and 192 mouse units, and reported high excretion in another.

Adrenal function. In the later stages of the disease the patients are lethargic and asthenic, and have a curious mental apathy. It is not uncommon to find patients in the late stages of the disease who have never sought medical advice. The asthenia is not comparable with that seen in Addison's disease. In no patient have we seen abnormal pigmentation. Tests for adrenal function can be divided into three categories, (1) electrolyte estimations, (2) tests of carbohydrate metabolism, and (3) tests of 17-ketosteroid excretion.

1. The plasma-chloride and serum-sodium were estimated in five patients, and the serum-potassium in three. The results were normal (Table I). The

TABLE I

Blood Electrolyte Levels

Case	*Plasma-chlorides (as NaCl, mg./100 ml.)*	*Serum-sodium (mg./100 ml.)*	*Serum-potassium (mg./100 ml.)*
Normal	570 to 620	325 to 350	16 to 20
E. B.	556	335	..
J. B.	600, 590	332	17·5
D. G. H.	580	342	..
F. S.	580, 600	340	16
F. A. M.	570, 556	327	17

TABLE II

Water Excretion Test

Case	*Volume of night urine (ml.)*	*Greatest volume of hourly urine (ml.)*	*Index*
E. B.	435	315	38
J. B.	300	210	35
F. S.	360	270	31

water excretion test (Robinson, Power, and Kepler, 1941) was performed on three patients. All had a delayed diuresis after the ingestion of a large volume of fluid, but the indices derived from applying the formula in the second part of the test were normal (Table II). An index of less than 25 in this test, if nephritis has been excluded, is a probable sign of adrenal cortical failure. The potassium-resistance test (Cutler, Power, and Wilder (1938) was performed in one case (F. A. M.). The urinary chlorides on the third morning of the test were 180 mg. per 100 ml. (as Cl′). This result is equivocal; normal patients excrete less than 125 mg. per 100 ml. in this specimen, and patients with Addison's disease more than 225 mg. per 100 ml.

2. Adrenal cortical hormones play an important part in carbohydrate metabolism. They accelerate the breakdown of tissue-protein to glucose in response to hypoglycaemia, and are thereby largely responsible for the rapid return of the blood-sugar to normal after an induced hypoglycaemia. This process is important in the regulation of fasting blood-sugar values. The glucose-tolerance and insulin-tolerance tests are methods of testing this function of the adrenal cortex. The standard two-hour tolerance test with 50 gm. oral glucose was used. Insulin tolerance was tested by the method of Fraser, Albright, and Smith (1941). Sugar determinations were made by the micro-method of Folin and Wu, with capillary blood. The results are given in Tables III and IV, and

TABLE III

Glucose-tolerance Test

	Blood-sugar (mg./100 ml.)					
Case	*Fasting*	*½ hr.*	*1 hr.*	*1½ hr.*	*2 hrs.*	*2½ hrs.*
E. B.	71	96	131	148	129	..
J. B.	65	120	135	130	85	..
R. F. H.	80	115	90	75	70	..
D. G. H.	83	140	96	69	72	82
F. S.	80	160	130	130	90	..
F. A. M.	98	125	135	139	130	124
	85	112	120	140	134	118

TABLE IV

Insulin-tolerance Test

	Blood-sugar (per cent. of fasting value)						
Case	*Fasting (mg./100 ml. in parentheses)*	*20 min.*	*30 min.*	*45 min.*	*60 min.*	*90 min.*	*120 min.*
E. B.	100 (70)	71	55	70	73	105	117
J. B.	100 (75)	80	53	80	87	75	100
R. F. H.	100 (76)	80	60	66	68	102	105
F. S.	100 (90)	72	50	78	84	89	90
F. A. M.	100 (106)	64	58	48	72	83	92
	100 (100)	72	41	37	77	110	105
E. L. K.	100 (106)	59	43	57	63	70	120

are on the whole normal. The glucose-tolerance tests of the patients E. B. and F. A. M. show a delayed return to normal sugar levels. F. A. M. had a delayed fall in the blood-sugar level after insulin. Similar insulin-tolerance curves have been reported in myxoedema (Fraser and Smith, 1941). It is interesting to note that this patient (F. A. M.) showed other symptoms of myxoedema.

3. The level of neutral urinary 17-ketosteroids is considered to be an index of the elaboration of androgenic hormone by the adrenal cortex in the female and by the adrenal cortex and the testicles in the male. The method used for the assay of 17-ketosteroids was that described by Fraser, Forbes, Albright, Sulkowitch, and Reifenstein (1941), in which spectrophotometric correction is made for extraneous colours. A Coleman no. 11 spectrophotometer was used.

By this method we obtained results similar to those published by the above authors: we found the excretion of 17-ketosteroids in normal men (six cases) to be 6·9 to 17·0 mg. in 24 hours, in normal women (14 cases) 3·8 to 12·5 mg. in 24 hours, and in Addison's disease (five women) and panhypopituitarism (10 cases) less than 1 mg. in 24 hours. The 24-hour excretion of neutral 17-ketosteroids was estimated in all our nine patients. Some of these cases have been reported elsewhere (Caughey, 1946). The results are given in Table V, and

TABLE V

Case	*17-ketosteroid excretion (mg. in 24 hrs.)*
E. B.	1·8
J. B.	1·2
R. F. H.	2·5, 4·5
D. G. H.	4·2, 5·5
C. C. W.	1·7
E. L. K.	4·8
F. A. M.	1·0, 0·4, 1·1, 1·3
P. H.	2·3
F. S.	3·1

are in general well below normal limits. Patients in whom the disease was advanced had excretions approaching those found in panhypopituitarism. Benda and Bixby (1947) determined the 24-hour excretion of 17-ketosteroids in five patients with dystrophia myotonica, and found values of 5·4, 8·0, 6·6, 4·8, and 2·8 mg. These values are higher than those reported in this paper, but are still below the normal values found by their method.

Thyroid function. The basal metabolic rate and serum-cholesterol levels were estimated in seven patients (Table VI). Waring, Ravin, and Walker (1940)

TABLE VI

Case	*Basal metabolic rate (per cent.)*	*Serum-cholesterol (mg. per 100 ml.) (normal, 120–220 mg./100 ml.)*
E. B.	−4	310
J. B.	+9	200
R. F. H.	−12, −8	180
D. G. H.	+38, +27	210
C. C. W.	+10	..
E. L. K.	..	180
F. S.	−9	205, 280
F. A. M.	−34, −48	335, 360

reported the basal metabolic rate and blood-cholesterol level in seven of their patients. They found, as a rule, low basal metabolic rates and normal cholesterol levels. Only two of our patients had abnormally low basal metabolic rates, but raised cholesterol levels were more frequent and appeared to parallel the severity of the condition. The patient D. G. H., whose basal metabolic rate was raised and serum-cholesterol normal, had an auricular flutter.

Parathyroid function. The similarity between the cataract occurring in dystrophia myotonica and that occurring in the tetany of hypoparathyroidism has been noted by many workers, and calcium metabolism has therefore been

studied in the former condition. Waring, Ravin, and Walker (1940) reported normal serum-calcium and serum-phosphorus levels in all their patients, and Milhorat and Toscani (1939) reported a normal calcium and phosphorus balance in one patient whom they examined. We determined the serum-calcium and serum-phosphorus levels in most of our patients, and in some cases estimated the alkaline phosphatase (Table VII). The results were on the whole normal.

TABLE VII

Case	*Serum-calcium (mg./100 ml.)*	*Serum-phosphorus (mg./100 ml.)*	*Plasma alkaline phosphatase (King-Armstrong units) (normal, 4–13)*
E. B.	10·3	4·0	8·0
J. B.	10·7, 9·9	2·0, 3·0	6·9
R. F. H.	10·7	3·6	3·2
D. G. H.	10·4	3·2	6
C. C. W.	10·8	..	..
E. L. K.	10·8	..	..
F. S.	10·1	2·2	4·0
F. A. M.	10·7, 10·5, 9·1	4·0, 3·3	17, 22

Since serum-calcium levels as low as those occurring in tetany due to hypoparathyroidism have never been recorded in a patient with dystrophia myotonica, and since no abnormality in calcium or phosphorus metabolism has yet been demonstrated, it appears that decreased parathyroid function is not a factor in this disease. The patient F. A. M., who had a raised plasma-phosphatase, had well-developed hyperostosis frontalis. Skull X-rays of three of our patients (E. B., J. B., and P. H.) showed a resemblance to Paget's disease. Plasma alkaline phosphatase was determined in two of these patients, and was normal. These findings are against the coexistence of Paget's disease, in which high alkaline phosphatase levels would be expected.

Discussion

This paper records a study of the endocrine changes which are so prominent a feature of the fully developed syndrome of dystrophia myotonica. Gonadal atrophy is the most striking of these changes, and has been described by the majority of observers. It is shown in the male by the size and softness of the testicles, atrophy of the prostate, loss of sexual power and libido, and frequent celibacy, and in the female by menstrual irregularities and infertility. Testicular biopsies performed on two of our patients showed almost complete degeneration of the seminiferous tubules and a decrease of the interstitial cells of Leydig. Since the skeletal proportions were normal, it is apparent that the hypogonadism must have developed after puberty. In the male the normal size of the penis and scrotum, and the male character of the voice, also pointed to an onset later than puberty. The assay of urinary follicle-stimulating hormone in patients with gonadal atrophy gave uniformly raised values. The raised excretion of follicle-stimulating hormone is strong evidence in favour

of a primary gonadal failure, and places these patients in the adult hypergonadotrophic hypogonadal group of Heller and Nelson (1948). The excretion of neutral 17-ketosteroids was estimated in all the cases described, and was uniformly lower than normal. Four patients excreted less than two mg. in 24 hours. These included three males, all of whom showed pronounced gonadal atrophy. Values of this order are too low to be explained merely by the asthenia present, and must be due to a degeneration both of the androgenic cells of the adrenals and of the Leydig cells of the testes, comparable to that found in panhypopituitarism. Female sufferers from the disease do not show the striking degrees of hypogonadism which are found in males. Here again we can postulate primary atrophy of the androgenic cells of the adrenals, with a normal ovarian and adrenal 'corticoid' function. Since androgenic hormone stimulates nitrogen-retention and muscle-growth, it was considered worth while to treat some of our patients with testosterone. Implants and injections in three patients gave disappointing results. It is notable that one (F. A. M.) developed gynaecomastia after this treatment. Waring, Ravin, and Walker (1940) treated some of their patients in the same way, but could detect little benefit. The same authors reported frequent myxoedema in their patients with low basal metabolic rates. Only two of our patients showed definite signs of myxoedema; both were in an advanced stage of the disease, and had low metabolic rates and raised serum-cholesterol levels. One of them showed the delayed response to insulin which has been reported in myxoedema. The resemblance of myotonia to tetany, and the almost invariable presence of cataract, have suggested to many observers a reduced function of the parathyroid glands. Serum-calcium and serum-phosphorus levels were estimated in the present series, and were found to be normal. Similar examinations have been made by many other workers, and in all cases normal results have been reported. There is therefore no direct evidence that the parathyroid glands are affected.

In the light of the foregoing results we are in a better position to assess the part played by the pituitary. The increased production of follicle-stimulating hormone by the pituitary absolves it from any responsibility for the presence of hypogonadism. The electrolyte and carbohydrate functions of the adrenal glands were, on the whole, normal in our patients, so that normal production of adrenotrophic hormone by the pituitary can be assumed. The part played by the pituitary in the presence of myxoedema has not been elucidated. The decrease in the metabolic rate following castration and adrenalectomy is well known, and is part of the general adaptation of the organism. Similar factors probably operate in dystrophia myotonica. Patients in an advanced stage of the disease, who show symptoms of myxoedema, are senile through muscle-wasting and loss of androgenic hormones. There is evidence that the pituitary is working subnormally in these patients. The excretion of follicle-stimulating hormone is not as high as that found in some types of primary hypogonadism of comparable severity. The low normal water-excretion tests and the equivocal tests of potassium-resistance lend support to the theory of a decreased production, though within normal limits, of adrenocorticotrophic hormone by the

pituitary. The myxoedema may be secondary to this general depression in pituitary function.

We are indebted to Dr. E. G. Sayers for giving us access to some of his patients, to Dr. H. L. Bowell for his radiological reports, to Mr. W. A. Fairclough for his opinion of the ophthalmological findings, to Dr. R. H. Caughey for his revision of the case reports, and to others who helped in the preparation of the paper.

Summary

The state of the endocrine functions is reported in nine cases of dystrophia myotonica. Our observations include:

1. A small sella turcica, thickening of the calvarium, and hyperostosis interna. These we regard as variable features of the disorder.
2. Gonadal atrophy in five cases, with raised excretion of follicle-stimulating hormone.
3. Normal electrolyte and carbohydrate function of the adrenal cortex.
4. Uniformly low 17-ketosteroid excretion.
5. Myxoedema in two cases.
6. Normal parathyroid function.

Evidence is presented that the primary glandular defect is atrophy of the androgenic cells of the testes and adrenal cortex.

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FIG. 1. Case 1 (F.A.M.)

FIG. 2. Case 7 (E.B.)

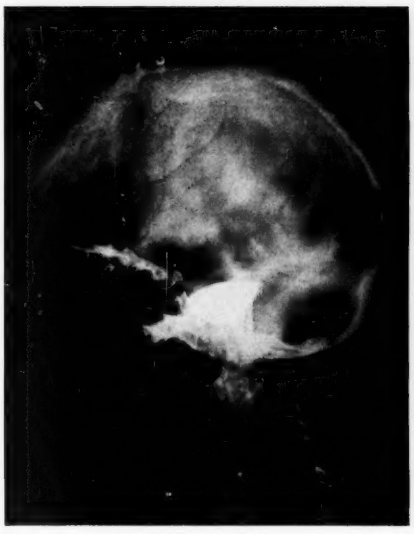

FIG. 3. Case 8 (J.B.)

FIG. 4. Case 9 (F.S.)

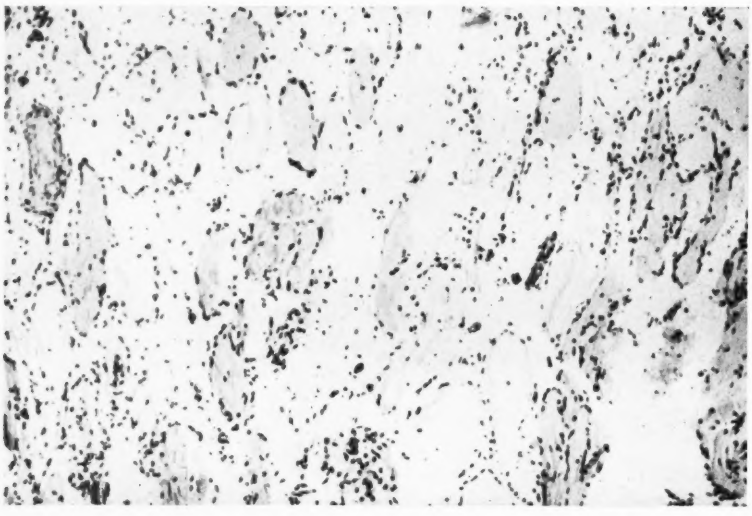

FIG. 5. Case 1 (F.A.M.). Testicular biopsy (× 100). Atrophy of seminiferous and interstitial elements almost complete.

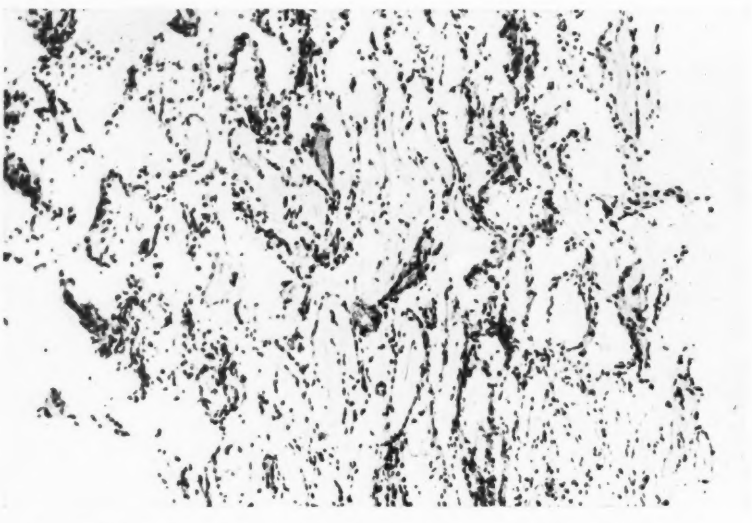

FIG. 6. Case 8 (J.B.). Testicular biopsy (× 100). Atrophy of seminiferous tubules almost complete. The interstitial cells are identified with difficulty and appear degenerate.

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THE EFFECT OF EPHEDRINE IN ASTHMA AND EMPHYSEMA[1]

By A. G. W. WHITFIELD, W. MELVILLE ARNOTT, and J. A. H. WATERHOUSE

(From the Departments of Medicine and Medical Statistics, Queen Elizabeth Hospital, Birmingham)

A quarter of a century ago Miller (1925) first called attention to the capacity of ephedrine to relieve the bronchial spasm of asthma. Middleton and Chen (1927) from a study of 25 asthmatics confirmed Miller's findings, and pointed out that the efficacy of the drug varied from case to case, approximately one-third of their patients obtaining no relief. The employment of ephedrine in the treatment of asthma rapidly became current practice and when, a few years later, Chen and Schmidt (1930) published their monograph on ephedrine and related substances, they were able to quote a long series of publications emphasizing its therapeutic value in this disease. At the same time they stated that ephedrine relieved the dyspnoea of emphysema, and its use for this purpose was subsequently recommended by Alexander and Kountz (1936), Chandler (1940), Christie (1944*b*), and Herxheimer (1946). Christie suggested that it acted by relieving bronchospasm which was not clinically evident.

The changes in the total lung-volume and its subdivisions during a paroxysm of asthma, and in emphysematous subjects, are well known. Hurtado, Fray, and McCann (1933), Hurtado, Kaltreider, Fray, Brooks, and McCann (1934), Aslett, Hart, and McMichael (1939), and Christie (1934, 1944*a*) all showed that in emphysema the volumes of air in the lungs at the end of a normal expiration (functional residual air) and at the end of a maximal expiration (residual air) are increased, that the vital capacity is decreased, and that these alterations are especially evident when the various subdivisions are considered as percentages of the total lung-volume. Hurtado and Kaltreider (1934) pointed out that similar changes occurred during a paroxysm of asthma, and that in such cases they were to a considerable extent reversible by the subcutaneous administration of adrenalin. Kountz and Alexander (1934) and Alexander and Kountz (1936) found that adrenalin also increased the vital capacity in patients with emphysema. Althausen and Schumacher (1927) in a small series of patients found an increase of vital capacity when an attack of asthma was relieved by ephedrine; Herxheimer (1946) confirmed this fact in a larger series of cases, but found that doses of up to four grains were often required, and about one-fifth of his subjects either were hypersensitive to the drug or failed to improve even with large doses. We have been unable to find any reference in the literature to

[1] Received May 4, 1950

the effect of ephedrine on the total lung-volume and its subdivisions in cases of emphysema, and previous quantitative investigations in cases of asthma all appear to have been limited to the effect of the drug on vital capacity. The object of this paper is to record the effect of the oral administration of the drug on the total lung-volume and its subdivisions in normal subjects, in patients with emphysema but without clinical evidence of bronchospasm, and in patients with asthma. The effect of ephedrine on the type of respiration as recorded by spirometry has also been investigated in these three groups, and a note of the findings is included.

Method

The vital capacity, complemental air, and reserve air were determined in the usual way on a Benedict-Knipping spirometer. The functional residual air was measured with the same apparatus, using the closed-circuit constant-volume hydrogen dilution method described by McMichael (1939–42). In the later part of the investigation helium was used instead of hydrogen. The type of respiration was recorded on a Benedict-Roth spirometer writing on a Brodie-Starling kymograph, the subject breathing quietly in and out of the spirometer for about three minutes. The tidal-air record thus obtained was kept level by feeding oxygen into the spirometer at the rate at which it was being absorbed by the patient. By these methods the total lung-volume and all its subdivisions were determined, and a record of the type of respiration was made for each subject before, and half to one hour after, an oral dose of ephedrine. In view of the well-known tendency to the development of ephedrine tolerance, recently emphasized by Herxheimer (1946), particular care was taken to ensure that none of the subjects took ephedrine for several days before the lung-volume estimation and tidal-air tracings were made.

Results

1. *Normal subjects.* The criteria of normality used were that the subject had had no significant respiratory, cardiovascular, or blood disease, had no symptoms or abnormal physical signs at the time of examination, and had a normal chest X-ray. The lung-volume of eight normal subjects was determined in the sitting posture. The dose of ephedrine given was half a grain, except in two instances where a dose of one grain was employed. A statistical analysis of the results obtained is shown in Table I, from which it will be seen that the drug produced no significant alteration in the total lung-volume or in any of its subdivisions. The effect of ephedrine on the type of respiration as shown in tidal-air tracings was examined in seven normal subjects, doses of one grain being administered in each instance. Though several of the subjects experienced side effects of which palpitation, tremulousness, headache, and nausea were the most frequent, the only alteration apparent in the spirographic pattern was some increase in the depth of respiration (Table IV).

2. *Emphysematous subjects without bronchospasm.* The criteria used for the diagnosis of emphysema were the presence of chronic cough and exertional

dyspnoea, the presence of some or all of the classical physical signs of the disease, the characteristic radiological changes, and a high ratio of residual air to total lung-volume. Although asthma had clearly played an aetiological part in some of the patients, none were asthmatic at the time of examination, and no rhonchi

TABLE I

Effect of Ephedrine on the Lung-volume of eight Normal Subjects

	Division of lung-volume	*Mean before drug*	*Mean after drug*	*Mean difference*	*t*	*P*
Absolute values in litres	Total lung-volume	6·21	6·14	−0·07	0·830	0·43
	Vital capacity	4·56	4·61	+0·05	0·815	0·41
	Complemental air	3·01	3·07	+0·06	0·774	0·46
	Reserve air	1·55	1·54	−0·01	0·156	0·88
	Functional residual air	3·21	3·05	−0·16	0·941	0·38
	Residual air	1·65	1·53	−0·12	0·998	0·35
Percentage of total lung-volume	Vital capacity	73·0	74·5	+1·5	0·932	0·39
	Complemental air	48·3	49·8	+1·5	0·849	0·42
	Reserve air	24·8	24·8	0	0	..
	Functional residual air	51·8	50·3	−1·5	−0·849	0·42
	Residual air	27·0	25·5	−1·5	−0·932	0·39

TABLE II

Effect of Ephedrine on the Lung-volume in 16 Cases of Emphysema Without Bronchospasm

	Division of lung-volume	*Mean before drug*	*Mean after drug*	*Mean difference*	*t*	*P*
Absolute values in litres	Total lung-volume	5·86	5·71	−0·15	1·186	0·25
	Vital capacity	2·82	2·81	−0·01	0·048	0·96
	Complemental air	1·99	1·94	−0·05	0·831	0·42
	Reserve air	0·82	0·87	+0·05	0·525	0·62
	Functional residual air	3·87	3·77	−0·10	0·989	0·34
	Residual air	3·05	2·90	−0·15	1·331	0·20
Percentage of total lung-volume	Vital capacity	48·2	34·6	−13·6	1·469	0·18
	Complemental air	33·5	26·3	−7·2	0·813	0·44
	Reserve air	14·7	8·3	−6·4	0·778	0·46
	Functional residual air	66·5	73·7	+7·2	−0·813	0·44
	Residual air	51·8	65·4	+13·6	−1·469	0·18

were audible on auscultation. In order to determine whether ephedrine altered the lung-volume, 16 patients satisfying these criteria were examined in the sitting posture before and after the drug. Doses of half a grain were given to three, and one grain to the remaining 13. A statistical analysis of the results obtained is shown in Table II, from which it will be seen that neither the total lung-volume nor any of its subdivisions was significantly altered. Six of the patients claimed some degree of subjective relief. Herxheimer (1946) stated that in many cases of emphysema much larger doses of ephedrine than those usually given were necessary to produce improvement. We therefore determined the lung-volume of six of our patients before and after doses varying from two-and-a-half to four grains. It will be seen from the statistical analysis of the results shown in Table III that even this dosage failed to produce any alteration

in the total lung-volume or in any of its subdivisions. Furthermore it was clear that doses of this magnitude could have no practical therapeutic value, as in all our subjects they produced marked nausea, headache, trembling, palpitation, and faintness. It must be added that probably none of Herxheimer's patients

TABLE III

Effect of Large Doses of Ephedrine on the Lung-volume in six Cases of Emphysema without Bronchospasm

Division of lung-volume	*Mean volume before drug (litres)*	*Mean volume after drug (litres)*	*Mean difference (litres)*	*t*	*P*
Total lung-volume	5·67	5·77	+0·10	0·771	0·47
Vital capacity	3·20	3·20	0	0	..
Complemental air	2·07	2·04	−0·03	0·385	0·71
Reserve air	1·13	1·16	+0·03	0·702	0·51
Functional residual air	3·60	3·73	+0·13	1·001	0·36
Residual air	2·47	2·57	+0·10	0·818	0·44

would have satisfied our criteria for this group, as they all had 'a nearly continuous wheeze', and therefore almost certainly bronchospasm, at the time of examination. They would thus be more comparable with our third series of patients.

Cournand, Richards, and Darling (1939), in their study of graphic tracings of respiration in pulmonary disease, found that in emphysematous subjects spirograms showed retarded breathing especially during expiration, with a plateau at the height of inspiration and a plateau during the expiratory phase. We compared the tidal-air tracings that we obtained from 25 normal subjects with those obtained from 11 patients suffering from emphysema without bronchospasm. The mean respiration rate in the normal group was 14·9 per minute and in the victims of emphysema 19·1 per minute; the mean inspiration/expiration ratio of the normal subjects was 1/1·41, and that of the patients suffering from emphysema 1/1·25. This result suggests that breathing is in fact accelerated, and the expiratory phase shortened, in emphysema. Furthermore the normal subjects showed a plateau at the height of inspiration more constantly than, and an expiratory plateau as frequently as the emphysematous group. It would appear therefore that the spirographic characteristics described by Cournand, Richards, and Darling are neither peculiar to nor especially indicative of emphysema. We made tidal-air tracings of nine patients suffering from emphysema without bronchospasm before and after doses of from one to four grains of ephedrine. The results obtained are shown in Table IV. No alteration in the rate or depth of respiration, nor in the inspiration/expiration ratio, expiratory plateau, or 'peak' was evident after the drug.

A word of explanation is perhaps necessary regarding the methods that we have employed in comparing the various groups of tidal-air tracings. The rate and depth of respiration and the inspiration/expiration ratio are of course capable of precise measurement, and have been compared by the customary statistical procedures. The 'peak' and expiratory plateau cannot be so treated,

and for comparative purposes were therefore put into one of four grades according to their appearance. The grades used for the 'peak' were very flat, flat, medium, and sharp; for the expiratory plateau, constant and marked, constant, frequent, and occasional or 'trace'. A shift of one, two, or three grades was made

TABLE IV

Effect of Ephedrine on Type of Respiration as Recorded Spirographically

Group of subjects	*Number of subjects*	*Respiration rate*	*Depth of respiration*	*Peak*	*Expiratory plateau*	*Inspiration/ expiration ratio*
Normal	7	No change	Increased	No change	No change	No change
Emphysematous	9	No change	No change	No change	No change	No change
Asthmatic	5	No change	Increased	Becomes sharper	Disappears	No change

TABLE V

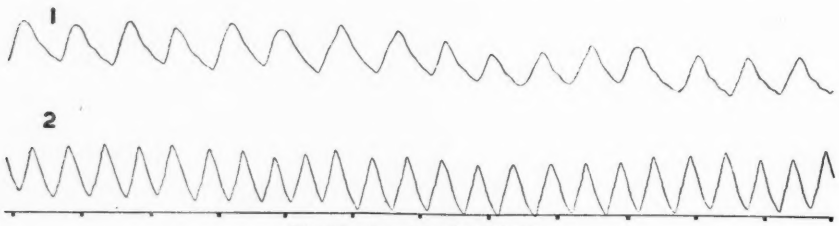
Effect of Ephedrine on the Lung-volume of 10 Emphysematous Subjects with Bronchospasm (i.e. Asthmatics)

	Division of lung-volume	*Mean before drug*	*Mean after drug*	*Mean difference*	*t*	*P*
Absolute values in litres	Total lung-volume	5·40	5·14	−0·26	0·907	0·38
	Vital capacity	2·11	2·53	+0·42	4·022	0·004
	Complemental air	1·52	1·71	+0·19	3·771	0·006
	Reserve air	0·59	0·82	+0·23	2·742	0·025
	Functional residual air	3·88	3·43	−0·45	1·656	0·14
	Residual air	3·29	2·61	−0·68	2·305	0·05
Percentage of total lung-volume	Vital capacity	39·2	49·9	+10·7	3·851	0·005
	Complemental air	28·1	34·2	+6·1	3·518	0·008
	Reserve air	11·1	15·7	+4·6	2·749	0·025
	Functional residual air	71·9	65·8	−6·1	−3·518	0·008
	Residual air	60·8	50·1	−10·7	−3·851	0·005

the quantitative basis on which statistical change in these spirographic features was assessed.

3. *Asthmatic subjects.* The patients whom we used for this part of the investigation were all obviously asthmatic at the time when their first lung-volume determination and tidal-air tracings were made. By 'obviously asthmatic' we mean that they were dyspnoeic, using their accessory respiratory muscles, audibly wheezing, conscious of constriction and tightness in the chest, and on auscultation were 'full of rhonchi'. All the patients had in addition considerable emphysema; six of the nine used for lung-volume determinations, and three of the five used for tidal-air tracings, had variable degrees of chronic bronchitis. The dose of ephedrine used was one grain in each case except one, in which a dose of two-and-a-half grains was given before the second lung-volume determination. In this particular instance the larger dose was given because the patient's respiratory distress was alarmingly severe. All the patients claimed subjective relief from the drug, and showed an obvious clinical reduction of dyspnoea. A minority became completely comfortable, and rhonchi were no longer audible on auscultation. A statistical analysis of the effect of the drug on the lung-volume is shown in Table V, from which it will be seen that after

ephedrine there is a highly significant increase in the absolute and percentage values of the vital capacity and complemental air, and a significant increase in the absolute and percentage values of the reserve air. The absolute value of the residual air is decreased to a degree which is just significant, but this diminution becomes highly significant when the percentage values are considered. Similarly



1. TIDAL AIR TRACING TAKEN WHEN ASTHMATIC.
2. TIDAL AIR TRACING TAKEN 1 HOUR AFTER 1 GR. OF EPHEDRINE.

Spirogram of an asthmatic subject.

the functional residual air shows a highly significant diminution in its percentage value, but the decrease in its absolute value is not significant. The total lung-volume shows no alteration. The effect of ephedrine on the spirographic pattern of asthmatic subjects is shown in Table IV. It produces an increase in the depth of respiration, makes the 'peak' sharper, and causes the expiratory plateau to disappear. A typical example is shown in the Figure.

Discussion

The changes which we have observed in the clinical state, in the lung-volume, and in the tidal-air tracings of asthmatic subjects after the oral administration of ephedrine, indicate that the beneficial effect of the drug is associated (1) with relief of bronchospasm, (2) with alterations in the divisions of lung-volume, viz. an increase in vital capacity affecting both complemental and reserve air, and a decrease in functional residual air and residual air, and (3) with an alteration in the type of respiration. Although relaxation of bronchial muscle-tonus and the dispersal of bronchial mucosal oedema, each in unknown proportion, seem to be key mechanisms, there may possibly be other factors such as changes in the volume of blood in the lungs. There is evidence (McMichael and McGibbon, 1939–42; Whitfield, Waterhouse, and Arnott, 1950) suggesting that an increase in cardiac output and in the volume of pulmonary blood, such as occurs in assuming the supine position, may explain some of the concomitant changes in the divisions of lung-volume. Although two of these changes—a decrease of functional residual air and of residual air—are also features of the ephedrine effect, they seem unlikely to be due to an increase of cardiac output, such as might easily be caused by a sympathomimetic amine, because the effect is not produced in normal subjects or in emphysematous subjects without broncho-

spasm. In brief, we consider that the beneficial effect, and also the concomitant changes, are due to the relief of broncho-constriction. Conversely, we have been unable to obtain any objective evidence that ephedrine, even in large doses, produces any alterations in pulmonary behaviour where bronchial constriction of the asthmatic type is absent.

We are indebted to Mr. A. C. Pincock for valuable technical advice and assistance, to Mr. T. F. Dee for reproduction of the Figure, and to Imperial Chemical Industries for a grant towards expenses.

Summary

1. The lung-volume before and after oral administration of ephedrine has been determined in eight normal subjects, in 16 patients suffering from emphysema without bronchospasm, and in nine emphysematous patients who were clinically asthmatic before the drug was administered.

2. The drug produced no alteration of total lung-volume or of any of its subdivisions either in the normal subjects or in the patients who had emphysema without bronchospasm.

3. The patients who were clinically asthmatic before the drug was administered showed subjective and objective relief of their respiratory distress, an increase of vital capacity, complemental air, and reserve air, a decrease of functional residual air and residual air, and no change of total lung-volume.

4. Doses of two-and-a-half to four grains of ephedrine had no effect on the lung-volume of emphysematous subjects who were not clinically asthmatic, and produced distressing side effects.

5. The oral administration of ephedrine did not alter the spirographic pattern either in seven normal subjects or in nine patients who were emphysematous but not asthmatic. Five patients suffering from emphysema, who were asthmatic before ephedrine was administered, showed after its administration an increased depth of respiration, a sharper 'peak', and a disappearance of the expiratory plateau.

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616.831.55–002.151

WERNICKE'S ENCEPHALOPATHY[1]

By ERIC K. CRUICKSHANK

(From the Department of Medicine, University of Aberdeen)

It has been recognized for many years that pathological changes in the central nervous system may occur in patients dying from beri-beri. Bentley (1893), reporting 19 cases, described the brain and its membranes as congested, and Wright (1901) noted changes in the cells of the nuclei of the medulla. They did not comment on any other intracerebral lesion. In 1898 Correa de Bittencourt, in a paper on the ocular disturbances in beri-beri, recorded haemorrhages in the optic nerves and chiasma, corpora quadrigemina, and occipital lobe, found in sufferers from fatal beri-beri who had complained of defective vision. Bälz and Miura (1905) stated that diplopia from paralysis of the sixth cranial nerve and horizontal nystagmus were very infrequent complications of beri-beri, but they did not describe any pathological changes in the brain to account for these findings. Blindness or 'beri-beri amblyopia' was described by early Japanese writers on beri-beri, and Yamaguchi referred to descriptions in Japanese by Kono in 1895 and Ichihara in 1902 (Yamaguchi, 1909). Kagoshima (1918) found diffuse degeneration of the optic nerves. None of these Japanese writers mentioned nystagmus, strabismus, or other evidences of cerebral damage.

It is only during the last 15 years that a relationship has been observed between vitamin B_1 deficiency and a disorder of the central nervous system first described by Wernicke in 1881 and named 'encephalitis haemorrhagica superior'. The syndrome now bears Wernicke's name, and he described it as a disease affecting the nuclei of the nerves of the eye-muscles and leading to death in a few days. The clinical signs are paralysis of the eye-muscles, a reeling gait, and disturbances of consciousness. The pathological findings in Wernicke's original cases were punctate haemorrhages in the vessel-sheaths in the tissue lining the third ventricle, in the corpora quadrigemina, and in the retinae. He regarded the process as inflammatory. Three cases were described. Two of the patients were chronic alcoholics, and one was a young woman who had recovered from sulphuric acid poisoning (Jacobäus, 1894). Little attention was given to the disorder until Gamper (1928) published a detailed account of the pathology, and further accounts appeared in German literature for a few years thereafter (Creutzfeldt, 1928; Ohkuma, 1930; Neubürger, 1931 *a*, *b*; Bodechtel and Gagel, 1931; Kant, 1932). The histological changes described by Gamper were a selective distribution of focal lesions throughout the grey matter of the brain-stem, consisting of hyperaemia sometimes accompanied by small haemorrhages,

[1] Received April 4, 1950.

endothelial and mesenchymal vascular proliferation, and a varying degree of glial proliferation, without inflammatory infiltration and with relatively slight evidence of damage to nerve-cells. The localization of the lesions was characteristic; they were constant and most marked in the corpora mamillaria and less constant in the other hypothalamic nuclei. In the midbrain they were frequently seen in the peri-aqueductal grey matter, involving the oculomotor nuclei. Nothing characteristic was found in the cerebral cortex. Gamper, and the other workers referred to above, regarded alcohol as the important aetiological agent, and Bender and Schilder (1933), after reviewing the clinical features and pathological findings in seven cases of Wernicke's syndrome, suggested that the condition should be called 'encephalopathia alcoholica', as alcohol appeared to be the main causative factor. Wechsler (1932) appears to have been the first to suggest that the syndrome resulted from vitamin deficiency secondarily induced by chronic alcoholism, although he offered no proof for this suggestion. Shattuck (1928) suggested that alcoholic peripheral neuritis was 'caused chiefly by failure to take or assimilate food containing sufficient quantity of vitamin B . . . and might properly be regarded as beriberi'. In 1935 Strauss showed that 'alcoholic' peripheral neuritis improved markedly on the administration of yeast by mouth and vitamin B concentrates and liver extract parenterally, although the patients still consumed large quantities of alcohol. Jolliffe, Colbert, and Joffe (1936) produced evidence to support this conclusion. The conception was extended to include the polyneuritis of pregnancy (Strauss, 1936) and it was a short step to postulate a similar mechanism for Wernicke's syndrome. It was known that Wernicke's syndrome occurred in patients taking no alcohol. One of Wernicke's original patients was not an alcoholic, and petechial haemorrhages had been found in the brain and spinal cord of three patients who died from polyneuritis gravidarum (Berkwitz and Lufkin, 1932). All three were disturbed mentally. One had rapid nystagmus, and in one the haemorrhages were most abundant in the corpora mamillaria. A fourth patient who had similar symptoms, and who complained of diplopia although no ocular palsies were demonstrable, recovered. Tillman (1934) described retinal haemorrhages, and punctate haemorrhages in the region of the basal ganglia, in two fatal cases of polyneuritis gravidarum, and further cases were recorded by Wagener and Weir (1937). Tanaka (1934) in Japan had found the typical lesions in the brains of suckling infants who had died of an inexplicable cerebral disorder which he attributed to intoxication from the mother's milk. These were presumably cases of infantile beri-beri, as beri-beri was then rife among Japanese nursing mothers. Neubürger (1937) described three patients with chronic gastritis who before death had disturbances of consciousness and ocular palsies, and in whose brains the typical lesions were found *post mortem*. There was no history of chronic alcoholism. He considered that endogenous toxins were responsible, that these were elaborated in an abnormally functioning gut, and that a damaged liver was unable to detoxicate them. He discussed the possibility of nutritional deficiency as a cause, but discarded it in favour of the toxin theory. In 1939 Campbell

and Biggart described the pathological findings in 12 patients with Wernicke's encephalopathy, only one of whom had a history of alcoholism. They favoured the view that vitamin B_1 deficiency was an important factor in its production. Ecker and Woltman (1939) also reported a case associated with nutritional deficiency, and suggested that defective nutrition, probably a lack of vitamin, was the underlying factor in all cases of Wernicke's disease. They claimed to have cured some patients with large doses of B complex, but gave no case records.

Evidence was also accruing on the experimental side in favour of vitamin B_1 deficiency as the causative factor in Wernicke's syndrome. In 1931 Pappenheimer and Goettsch described foci of oedema, necrosis, and petechial haemorrhage, limited to the cerebellum, in chicks fed on a diet deficient in vitamin E and probably deficient in B_1; the intake of vitamin B_2 was adequate. Prickett (1934) observed in rats fed on a B_1-free diet foci of petechial haemorrhage or marked congestion, usually bilaterally symmetrical, in the pons, medulla, cerebellum, optic lobes, and cerebrum. Church (1935) noted perivascular haemorrhages in the region of the vestibular nuclei in B_1-deficient rats. Green in 1936 described a disease of foxes under the name of 'Chastek paralysis', characterized by loss of appetite, weakness, ataxia, spastic paralysis, and death. He postulated that the disease was due to vitamin B_1 deficiency. Later he was able to produce convincing evidence to support this view (Green, 1936; Green and Evans, 1940; Green, Carlson, and Evans, 1942). The deficiency resulted from the inactivation of vitamin B_1 in the diet by a substance present in uncooked fish, and could be prevented by large doses of the vitamin. The pathological lesions were bilateral and symmetrical small punctate haemorrhages in the floor of the fourth ventricle, in the corpora quadrigemina, in certain nuclei ventral and lateral to the aqueduct of Sylvius, in the thalamus, and in certain parts of the cerebral cortex. In 1938 Alexander, Pijoan, Myerson, and Keane produced pin-point haemorrhages within areas of subacute necrosis in the paraventricular and paramedian nuclei of the thalamus and in the nuclei of the eye-muscles, with significant regularity, in pigeons fed on a diet deficient in vitamin B_1 but otherwise adequate. If the birds were given vitamin B_1 these lesions did not appear. They pointed out that the lesions were very similar to those found in cases of Wernicke's syndrome in man. Alexander (1940) repeated the experiments, and came to the conclusion that histologically the lesions in the B_1-deficient pigeons were identical in their topographical distribution and in their morphological and histological characteristics with those of Wernicke's encephalopathy. He suggested that vitamin B_1 in small amounts is necessary for the integrity of the small cerebral vessels, that the lesions are the direct result of gross B_1 deficiency, and that peripheral nerve damage occurs with less severe degrees of deficiency.

Jolliffe, Wortis, and Fein (1941) reported 27 cases of Wernicke's syndrome. All showed mental confusion and ophthalmoplegia, and 24 of the patients were chronic alcoholics. In 25 peripheral neuritis was present and antedated the appearance of the ophthalmoplegia. They regarded this as evidence in favour

of Alexander's view that smaller quantities of aneurin are necessary for blood-vessel maintenance than for the peripheral nerves. They considered that Wernicke's syndrome results from the deficiency of several factors, particularly nicotinic acid and aneurin. The ophthalmoplegia in 19 of their cases improved markedly, or more often cleared entirely, when aneurin was given in adequate amounts. Nicotinic acid had no effect on the ophthalmoplegia in nine cases in which it was administered. Campbell and Russell (1941) described the clinical features of 21 cases of Wernicke's encephalopathy, in 12 of which the post-mortem findings had been previously reported. One of these patients was treated with 10 mg. of crystalline vitamin B_1 intramuscularly daily for nine days and made a dramatic recovery, the apathy, drowsiness, and ocular signs disappearing in a few days. The striking results of treatment with vitamin B_1 alone obtained by these authors and by Jolliffe and his fellow workers are strong evidence in favour of the view that B_1 deficiency is responsible for Wernicke's syndrome. The results of treatment given to the patients to be described later bears out this conclusion. One of these patients, and his response to treatment with crystalline B_1, have already been reported by de Wardener and Lennox (1947). Tissue from the brain of one fatal case was brought back to this country, and showed the typical naked-eye and microscopic appearances described by Campbell and Biggart (1939).

Case Records

Beri-beri first made its appearance among British prisoners of war in the hands of the Japanese in Changi camp, Singapore, a few weeks after the capitulation in February 1942. During the next few months there was a rapid increase in its incidence to a maximum of 10 fresh cases per 1,000 per month, the total camp population at that time being over 50,000. This was only to be expected, since the diet issued by the Japanese during the first seven months of imprisonment was grossly deficient in vitamin B_1. A detailed analysis of the total calories, protein, carbohydrate, fat, and vitamins of the diet during the three and a half years of captivity has been reported by Burgess (1946). That part of the analysis which relates to the cases recorded here is given in Table I. It will be seen that for the first seven months the ratio of vitamin B_1 to non-fat calories was below the critical level of 0·3 mg. per 1,000, short of which clinical evidence of vitamin B_1 deficiency may be encountered (Williams and Spies, 1938). During this time nearly 100 patients presenting the clinical features of Wernicke's encephalopathy were observed, and in those that died the typical punctate haemorrhages were found in the midbrain. The majority of the cases occurred in patients suffering from bacillary dysentery, and an account of the findings in 52 cases have been reported by de Wardener and Lennox (1947). Eight patients, however, in whom dysentery did not dominate the picture were under the author's care. The course of events in these patients can be most satisfactorily represented by the case histories, and these are detailed below.

Case 1. A. H., aged 28 years, was admitted to hospital on April 8, 1942, with the following history. Eighteen days previously he had developed diarrhoea, with five to six loose stools per day which contained no blood or mucus. Anorexia was the only other symptom. Eight days later he began to vomit after every meal. There was no abdominal pain, and the vomiting was effortless and without nausea or retching. Three days before his admission the diarrhoea had stopped, but anorexia and vomiting persisted, and at the same time he developed a severe retro-orbital headache, with dizziness which was sufficiently severe to make standing difficult. The next day he complained of blurring of distant

TABLE I

Diet in Changi Camp, 1942

	Mar.	*Apr.*	*May*	*June*	*July*	*Aug.*	*Sept.*	*Oct. 1–9*	*Oct. 10–31*	*Nov.*	*Dec.*
Protein (gm.)	41	40	45	50	47	43	48	50	83	85	67
Non-fat cals.	1,874	1,911	2,058	2,017	2,120	2,271	2,251	2,075	2,480	2,452	2,259
Total cals.	2,060	2,060	2,263	2,222	2,315	2,466	2,548	2,260	2,899	2,973	2,659
Vitamin B_1 (μg.)	390	405	593	732	551	488	678	953	1,119	1,246	1,159
Riboflavine (μg.)	498	434	470	566	517	484	555	559	905	890	824
Nicotinic acid (μg.)	6,809	7,001	11,097	14,299	10,997	8,489	11,194	15,366	19,180	20,782	18,588
B_1 (mg.) per 1,000 non-fat cals.	0·21	0·21	0·29	0·33	0·26	0·21	0·30	0·46	0·48	0·51	0·51
Riboflavine (mg.) per 1,000 total cals.	0·24	0·21	0·21	0·25	0·22	0·20	0·22	0·25	0·31	0·30	0·31
Nicotinic acid (mg.) per 1,000 total cals.	3·31	3·40	4·90	6·44	4·75	3·44	4·39	6·80	6·62	6·99	6·99
Williams and Spies:											
Vitamin B_1 (μg.)	316	341	526	587	424	393	559	842	1,075	1,161	1,053
(mg. per 1,000 non-fat cals.)	0·17	0·18	0·26	0·29	0·20	0·17	0·25	0·40	0·42	0·47	0·47

vision and 'haziness on looking to either side'. There were no other symptoms. On examination he was apathetic and gave the impression of extreme stupidity, but his platoon officer said he had been of average intelligence and a good worker. He answered questions in a loud voice, but there was no evidence of deafness. He had no fever, and showed evidence of dehydration. There was a coarse sustained nystagmus on looking to either side. Nothing else abnormal was found in the nervous system. The blood-pressure was 132/84. The fundi were normal, and there was no sugar or albumin in the urine. Lumbar puncture produced a normal cerebrospinal fluid not under increased pressure. The vomiting became less frequent, but he continued to complain of severe headache and dizziness. On April 10 his temperature rose to 100° F., the nystagmus was well marked, and two flame-shaped haemorrhages had appeared at the margin of the right optic disk, but there was no papilloedema. By April 13 he was stuporous, and refused to eat; the nystagmus was unchanged, and numerous haemorrhages had appeared in both fundi. On April 14 he became comatose, petechial haemorrhages appeared round his ankles and on his trunk, and he died that evening. Post-mortem examination showed healing dysenteric ulceration of the colon. The other organs were normal except the brain, which showed no engorgement or oedema, but numerous small punctate haemorrhages in the region of the corpora mamillaria. Dr. Lennox, the pathologist, had seen one previous case of Wernicke's encephalopathy, and made this diagnosis *post mortem*.

Case 2. T. B., aged 36 years, was admitted on April 9, 1942. He had been a coal-miner, and had good health in civil life. On March 2, 1942, he developed diarrhoea, with four to five stools in 24 hours, but no general symptoms. This lasted for a week. On April 5 he began to have effortless vomiting, not related to meals, and slight anorexia. Frequent vomiting continued till his admission, when nothing abnormal was found on examination. In the course of the next two days the vomiting ceased, but on April 13 his temperature had risen to

100° F. He was listless, drowsy, and apathetic, had vomited several times during the day, and looked ill. The only abnormality found on examination was a coarse lateral nystagmus to both sides. The next day he complained of severe headache. The cerebrospinal fluid was normal and not under increased pressure. On April 15 he developed bilateral sixth nerve paralysis and painless retention of urine. There were no other abnormal signs. He was mentally dull and slow, and occasionally disorientated. A diagnosis of Wernicke's encephalopathy was made the next day, after the post-mortem examination of Case 1. Two mg. of vitamin B_1 were given intravenously. In 24 hours the sixth nerve paralysis had disappeared. Two mg. of vitamin B_1 were given again, and in three days the nystagmus had disappeared. He became less drowsy and during the next week, when he received half an ounce of marmite three times a day, there was some improvement in his mental apathy. Two months later, when he was last seen, he was facile, dirty in his habits, and considerably below his previous mental level.

Case 3. G. W., aged 26 years, was admitted on April 10, 1942, with febrile symptoms and a history of malaria one month before. Malignant tertian parasites were found in his blood, and a course of atebrin, 0·1 gm. three times daily, was started. On April 16 his temperature had subsided, but he began vomiting effortlessly and frequently during the day. The next day the vomiting continued, and he became mentally confused and distressed, talked nonsense, and was restless. There was rapid lateral nystagmus to both sides. The confusion, vomiting, and nystagmus persisted until April 20. The cerebrospinal fluid was normal and not under pressure. He was given two mg. of vitamin B_1 intramuscularly. This was repeated next day when he showed considerable improvement, and by April 23 the vomiting had ceased and he was mentally much clearer. The nystagmus was still present. He could now take and retain half an ounce of marmite thrice daily. By April 27 he was mentally normal, although very thin and weak, and by May 2 the nystagmus had completely disappeared.

Case 4. P. J., aged 25 years, was admitted on April 9, 1942, with a history of benign tertian malaria six months before. Three weeks before admission he had had malaise and fever for two days, followed by mild diarrhoea for about a week, with no blood or mucus in the stools. After the diarrhoea had stopped he began to vomit after meals and in the mornings, and this had persisted till his admission. Gastric lavage and a fluid diet had no effect on the vomiting, and two litres of glucose-saline were given intravenously by drip. His temperature rose to 101° F. that evening. On April 18 he developed a moderately coarse bilateral nystagmus, slower to the right than to the left. He complained of slight deafness in the right ear. All the reflexes were present and equal. The vomiting continued, and by April 20 he showed mental dullness and marked nystagmus, and the knee- and ankle-jerks had disappeared. He was then given two mg. of vitamin B_1 intravenously, and this was repeated the next day. By April 23 the vomiting had stopped, and he was mentally normal. The nystagmus was still present and the knee- and ankle-reflexes absent. In one week, during which he was given one ounce of marmite daily, the nystagmus had disappeared, but the reflexes were still absent.

Case 5. O. C., aged 31 years, was admitted on April 13, 1942, with no history of previous illnesses; on several occasions during the previous two weeks he had noticed slight blurring of vision, but was otherwise well until four days before his admission, when he suddenly vomited in the morning after breakfast; since then he had vomited everything he had taken. Two days later he had

developed diplopia in all directions and a moderately severe retro-orbital headache. On examination he was lying with his eyes shut, but was mentally alert and co-operative. His breath smelled strongly of acetone. He had a bilateral internal strabismus, but on two occasions each eye deviated laterally for about one second, and showed coarse nystagmoid movements, when the other eye was shut. No other abnormality was demonstrable, and the blood-pressure was 108/64. There may have been some blurring of the margins of the optic disks. The cerebrospinal fluid was normal and not under pressure. The vomiting ceased for two days with strict rest in bed, but there was no change in the eye signs. On April 18 he began to make irrelevant remarks to the orderlies and to other patients. He rapidly became disorientated and confused, with hallucinations. Two mg. of vitamin B_1 were given intramuscularly. Two days later his mental condition had considerably improved, but some disorientation persisted, and his memory was poor. The strabismus had completely disappeared, and a rapid bilateral nystagmus was present. A further two mg. of crystalline vitamin B_1 were given intramuscularly on April 23 and April 25, and thereafter marmite, half an ounce thrice daily. He remained slightly confused and occasionally disorientated, but very co-operative and at times euphoric. A fine bilateral nystagmus persisted. On June 9, 1942, he did not know the year, month, or day of the week, said he just could not remember, and that 'things were all mixed up'. Confabulation occurred at times, and his attitude was one of placid contentment. The fine nystagmus was still present. He was discharged to his unit and shortly afterwards went to Thailand. His subsequent record has not been traced.

Case 6. W. G. W., aged 36 years, was admitted on April 15, 1942, with a history of moderately severe dysentery of one week's duration six weeks previously. Since then he had felt generally weak, his appetite had been poor, and he had had nausea and occasional vomiting. Three days prior to admission he began to vomit after every meal. The next day he developed a persistent 'deep' headache and giddiness on standing, and on the same evening diplopia appeared. On examination he was apathetic and wasted. There was no fever. The tongue was dry, red, and slightly atrophic. There was a slight right internal strabismus with defective lateral movement to both sides, diplopia, and a slow, swinging, wide-ranged, sustained nystagmus. No other abnormality was demonstrable. On April 17 he was given two mg. of vitamin B_1 intramuscularly. In 48 hours the diplopia had disappeared, and the vomiting had ceased. One ounce of marmite was given three times a day. His appetite returned, but he remained mentally dull and apathetic. His behaviour was childlike, but there were no hallucinations or disorientation. By May 15 he had gained weight, but there was little change in his mental state. The nystagmus was fine and rapid, and much less marked. His platoon officer stated that he had never been mentally alert, but that there was considerable deterioration. He was discharged to his unit, and unfortunately was not seen again.

Case 7. G. G., aged 27 years, was admitted on April 16, 1942, with the history that he had been well until one month before, when he began to vomit, particularly after meals of rice. There was anorexia and slight nausea. The vomiting was effortless; it stopped after five days, but the anorexia persisted. Two weeks prior to admission the vomiting began again. Ten days later he noticed that his vision was blurred, and vomiting occurred every half-hour. He then developed diplopia in all directions. There were no symptoms of fever, and in one month he had lost nearly three stone in weight. On examination he was dehydrated. There was vertical and coarse bilateral nystagmus, with

a slight right internal strabismus, although the eye movements appeared to be full in all directions. Diplopia was most marked on looking to the right. There were no other abnormalities, and the blood-pressure was 104/72. He was given two mg. of vitamin B_1 intramuscularly. The next day there was no vomiting, and by April 18 the diplopia and squint were no longer present. There was coarse nystagmus in all directions, but the vertical movement was finer and slightly rotatory. He continued to take marmite, half an ounce thrice daily, till April 30, and thereafter was given 24 Japanese vitamin B tablets a day instead. There was never any mental derangement. He gradually gained strength, but the nystagmus persisted, although it was more rapid. He was seen five years later; he had remained well, but the nystagmus was still present.

Case 8. J. H., aged 26 years, was admitted on April 17, 1942, in a confused, irrational state. The only information obtained was that he had had diarrhoea for two weeks about two months before, but none for the last month, and that he had been unable to walk for two days. On examination the temperature was 102° F. and the pulse-rate 130. The tongue was furred and moist. He was breathless on the least movement, and there was cyanosis of the lips, fingers, and feet. He was disorientated as to time and place. The pupils were small but equal, and reacted to light. There was a rapid, sustained nystagmus to both sides. The power in his arms was weak, the reflexes were present but diminished, and there was hypalgesia below the middle third of both forearms. There was marked weakness of all muscle groups in the legs. The knee-jerks and ankle-jerks were not elicited. Diminution of all forms of sensation extended from his toes to the middle third of his thighs. The plantar responses were flexor. The neck veins were not distended, and the heart was not clinically enlarged. The heart-rate was 154, the sounds 'tic-tac', and the blood-pressure 98/64. There was slight oedema of the ankles and shins. No other abnormality was demonstrable. He was given four mg. of vitamin B_1 intravenously. His condition rapidly deteriorated, and he died the next day. At post-mortem the only abnormal findings were a grossly dilated right heart and numerous punctate haemorrhages in the midbrain.

Discussion

An analysis of the clinical features of these cases is given in Table II. The onset in five was preceded by diarrhoea. This diarrhoea was relatively mild, and was an extremely common occurrence in the camp at this time. It was probably a precipitating factor. Frequent effortless vomiting, with anorexia, was the earliest symptom in all cases except one. Brain (1947) stated that the first symptoms of Wernicke's encephalopathy are psychological. But Neubürger (1937) in describing three cases, and Környey (1937) in describing two, reported persistent vomiting as a precursor of the encephalopathic signs, and Wagener and Weir (1937) commented on the frequency with which persistent vomiting precedes the appearance of neurological disorders. Anorexia, nausea, and vomiting occurred in 31 of the 52 cases described by de Wardener and Lennox (1947) and in each case were the earliest features to appear. The majority of the reported cases of Wernicke's syndrome (Jolliffe, Wortis, and Fein, 1941; Campbell and Russell, 1941; Környey, 1937; Brain, 1947) have occurred in chronic alcoholics, or in patients with carcinoma of the stomach or other chronic gastro-intestinal disorders, so that it is possible that vomiting

occurred but was attributed to the primary disease. Campbell and Russell (1941) did not comment on vomiting in the text of their paper, but a review of their 21 case-histories shows that in 11 the earliest feature was severe and persistent vomiting. In the present small series the vomiting occurred when there was little other evidence of gastro-intestinal disease, and for this reason and in view of its effortless nature it was probably cerebral, not gastro-intestinal

TABLE II

The Clinical Features of eight Cases of Wernicke's Encephalopathy

Figures represent the number of days prior (−) and subsequent (+) to the day of admission to hospital when each feature first appeared (0 = day of admission). 18 D 15 = diarrhoea, onset 18 days before admission, duration 15 days. 5–6/24 = five to six stools in 24 hours. R = recovery. P.R = partial recovery. M.T = malignant tertian malaria. B.T = benign tertian malaria. M = marmite.

Case number	1	2	3	4	5	6	7	8
Date of admission	8.4.42	9.4.42	10.4.42	9.4.42	13.4.42	16.4.42	16.4.42	17.4.42
Diarrhoea	18 D 15 5–6/24	13 D 7 4–5/24	.. ..	21 D 7 3–4/24	.. ..	42 D 7 +/24	.. ..	30 D 14 ..
Other diseases	..	..	M.T twice	B.T	..	..	..	..
Vomiting	−8	−4	+6	−14	−4	−3	−30	..
Headache	−3	+1	..	..	−2	−2	..	?
Dizziness	−3	..	..	..	..	−2	..	?
Blurring or diplopia	−2	+6	..	..	−2	−2	−4	?
Mental disturbances	0	+4	+7	+11	+5	0	..	0
Nystagmus	+	+	+	+	+	+	+	+
Squint	..	+	..	..	+	+	+	..
Other neurological abnormalities	..	Retention of urine	..	Knee- and ankle-jerks absent	..	..	..	Peripheral neuritis
Fever	+	+	..	+	..	..	..	+
Treatment	.. .. ..	4 mg. B_1 intrav. M ½ oz. t.i.d. ..	4 mg. B_1 intram. M ½ oz. t.i.d. ..	4 mg. B_1 intrav. M 1 oz. daily ..	6 mg. B_1 intram. M ½ oz. t.i.d. ..	2 mg. B_1 intram. M 1 oz. t.i.d. ..	2 mg. B_1 intram. M ½ oz. t.i.d. Jap. B 24 daily	4 mg. B_1 intrav. .. ..
Result	Died	P.R	R	R	P.R	P.R	P.R	Died

in origin. Nystagmus was the earliest sign to appear, and was usually present a few days after the onset of severe vomiting. It was observed in every case. Some clinical accounts of Wernicke's syndrome do not mention nystagmus. Campbell and Russell (1941) noted it in five of their 21 cases, but suggested that it might have been overlooked in others. Moreover, since a large proportion of the reported cases had ophthalmoplegia when first seen, any pre-existing nystagmus would have been obscured; 20 of Jolliffe's 27 patients had gross ophthalmoplegia. It is interesting to observe that the nystagmus was present in two of our patients after ophthalmoplegia had disappeared with vitamin B_1 therapy. In one of these there was also residual mental impairment; the other was mentally normal, but the nystagmus was still present when he was seen in this country five years later. None of the patients showed any ataxia or incoordination of the limbs. Severe vomiting and nystagmus, then, were the outstanding early features of the disease and, as its early recognition and treatment were all-important, they were regarded as justifiable indications for administration of some of the very limited stocks of vitamin B_1. This opinion

was borne out later when three further patients, with only these two features, recovered within 48 hours of receiving two mg. of vitamin B_1 intramuscularly.

Diplopia was present in five cases. It preceded the appearance of mental derangement in three of the four patients in whom these signs occurred together. It may be regarded as a warning signal of imminent mental disorder. It is the best recognized ocular manifestation of the syndrome, and all the eye muscles may be completely paralysed. The mental disturbances were of different forms, varying from dull apathy with mental retardation to confabulation, disorientation in space and time, and visual hallucinations. They are in keeping with the varied picture reported by other authors (Jolliffe, Wortis, and Fein, 1941; Alexander, 1940; Brain, 1947; de Wardener and Lennox, 1947; Campbell and Russell, 1941). The distressing aspect of this derangement was that it failed to disappear on treatment in three cases although normality was otherwise restored, and these men remained mental cripples as long as they were under observation. There are not yet many reports of the results of treatment of the syndrome with vitamin B_1, but Jolliffe, Wortis, and Fein (1941) noted the persistence of psychotic symptoms in 12 of 13 patients who survived, although the ocular manifestations had rapidly cleared with aneurin. Eleven of these 12 patients were chronic alcoholics. The other and less important features of our cases were moderately severe headache in four, fever for which no obvious cause could be found in four, appearing when the cerebral signs became marked, fundal haemorrhages in one, and retention of urine in one.

An important aspect was the absence of other signs of vitamin B_1 deficiency in six of the eight cases. Peripheral neuritis was present in 25 of 26 of Jolliffe's patients (Jolliffe, Wortis, and Fein, 1941) and in nine of the 21 described by Campbell and Russell (1941). De Wardener and Lennox (1947) noted signs of other forms of beri-beri in 47 of their 51 patients. Alexander (1940), as a result of his experimental work in pigeons, considered that smaller quantities of aneurin are necessary for blood-vessel maintenance than for peripheral nerves. This is supported by the findings of Jolliffe, Wortis, and Fein (1941) and de Wardener and Lennox (1947), and by the fact that the incidence of peripheral neuritis in the camp was very much higher than that of Wernicke's syndrome. The findings in the eight cases reported above are accordingly of peculiar interest, since manifestations of peripheral neuritis were present in only two. This would seem to suggest that the initial indications of vitamin B_1 deficiency show marked variation in different individuals; usually the peripheral nerves first show evidence of deficiency, but in other cases damage to the cerebral blood-vessels may occur alone, as in six of the eight cases described above. Moreover, the cases of Wernicke's syndrome observed in Changi Camp occurred relatively soon after incarceration, when the incidence of beri-beri was high. Dysentery and diarrhoea were rife in the camp, as it took some months to enforce adequate sanitary measures. The supply and equitable distribution of food were not fully established. With improvement in these conditions the incidence of beri-beri rapidly fell, although cases continued to occur, while no fresh cases of Wernicke's syndrome were observed. This may indicate that

Wernicke's syndrome is most likely to be met with when gross aneurin deficiency appears suddenly in a previously healthy community who have been receiving a good diet.

The rapid disappearance of the vomiting and ophthalmoplegia on treatment with two to four mg. of parenteral vitamin B_1 is the most striking feature of our cases, and is strong evidence that deficiency of B_1 alone is the all-important factor in the production of the syndrome. Had larger doses been available the mental derangement might have been more effectively dealt with, but this must remain a speculation. The residual nystagmus persisted in two cases and the mental symptoms in three, and in these patients irreparable damage may have occurred in the cerebral tissue before treatment was begun.

Summary

The literature of Wernicke's encephalopathy is reviewed. The clinical features of eight cases are described:

1. Vomiting and nystagmus were the most prominent early features. Ophthalmoplegia and mental disturbances occurred later in some cases.

2. Only two of the eight patients showed other evidence of vitamin B_1 deficiency.

3. Two patients died; in one the syndrome was not recognized and no specific treatment was given, and the other was almost moribund when vitamin B_1 was administered.

4. Small doses of vitamin B_1 given parenterally caused a dramatic cessation of vomiting and the disappearance of ocular paralysis.

5. Residual mental changes persisted in three cases, and nystagmus in two.

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616.71–006.441:615.3

THE BONE AND JOINT LESIONS IN ACUTE LEUKAEMIA AND THEIR RESPONSE TO FOLIC ACID ANTAGONISTS[1]

By ELLIS DRESNER

(From the Department of Medicine, Postgraduate Medical School, Ducane Road, London, W. 12)

With Plates 30 to 35

THE early manifestations of leukaemia in childhood are protean, and symptoms referable to the bones or joints may dominate the picture. Such symptoms may arise during the course of an illness in which the diagnosis of leukaemia has already been made, or they may be the presenting feature. Leukaemia in childhood is often aleukaemic, with no immature leucocytes in the peripheral blood. In addition, palpable enlargement of lymph-nodes and viscera may be minimal. It is not surprising, therefore, that in some cases of leukaemia presenting with anaemia, bone pains, arthralgia or joint swellings, and possibly haemic cardiac murmurs, the nature of the illness is not at first recognized, and a primary disease of the osteo-articular system is diagnosed. The condition most closely simulated is rheumatic fever, and cases of this kind are well documented (Baldridge and Awe, 1930; Poynton and Lightwood, 1932; Sutton and Bosworth, 1934; Bichel, 1948). Failure to respond to salicylates, the later appearance of leukaemic cells in the blood, or the development of radiological changes in the bones may then indicate the necessity of a bone-marrow biopsy for a correct diagnosis. Still's disease may be suggested by involvement of the finger-joints, together with moderate enlargement of the lymph-nodes and spleen and a blood picture of anaemia and relative lymphocytosis without leucocytosis (Conybeare, 1936; Silverman, 1948). Less commonly, severe involvement of the spinal column may be the principal osseous lesion, and may be clinically indistinguishable from spinal caries (Rolleston and Frankau, 1914). Congenital syphilis, scurvy, and osteomyelitis (Bonaba and Volpe, 1933) are further examples of mistaken diagnosis in the leukaemia of childhood with bone involvement. These lesions of bone fall into certain radiological patterns. The purpose of this paper is to describe their appearance in five cases of leukaemia in children and the effect produced on them by treatment with the folic acid antagonists 4-amino-pteroylglutamic acid (aminopterin) and 4-amino-N^{10}-methylpteroylglutamic acid (amethopterin). A more detailed study of the haematological effects of aminopterin in acute leukaemia in children and adults has been reported elsewhere (Dacie, Dresner, Mollin, and White, 1950).

[1] Received April 27, 1950

The Bone Lesions of Acute Leukaemia

The involvement of bone in leukaemia was noted soon after Virchow's original description of the disease in 1845. The early observations were clinical and anatomical, and mainly concerned osteolytic and destructive lesions (Heschl, 1855; Neumann, 1878), but osteosclerosis (Heuck, 1879; Schwarz, 1900) and periosteal proliferation (Eisenlohr, 1878) were also observed. Periarticular periosteal elevation with new bone formation was demonstrated radiologically by von Jaksch in 1901; in the belief that this was the primary lesion he named the condition 'periostitis multiplex with myelocythaemia'. Since these early observations were made, the widespread use of serial radiographs has led to a better recognition of leukaemic bone lesions, and it is now often possible to diagnose leukaemia from the radiographic appearance of the bones alone. The lesions are most frequent in children with acute or subacute leukaemia, and are rare in adults and in chronic leukaemias. Usually the leukaemia is lymphoblastic in type, and the peripheral blood aleukaemic. Baty and Vogt (1935) found bone changes in 30 of 43 leukaemic children. The majority of these 30 patients had an aleukaemic leukaemia, which was equally often lymphoblastic and myeloblastic in type. Baldridge and Awe (1930) found acute polyarthritis in 13 of 20 patients with lymphatic leukaemia. Snelling and Brown (1935) found that 12 cases of lymphatic leukaemia all showed bone changes at some time, and Landolt (1946) found bone changes in 29 out of 38 such cases. Kalayjian, Herbut, and Erf (1946) collected from the literature 144 cases of leukaemia with bone lesions in children; 138 were lymphatic and five were myeloid in type, and the majority were aleukaemic. To these they added two further cases, both in children suffering from aleukaemic lymphoblastic leukaemia. Of 40 leukaemic children examined radiologically by Dale (1949), 29 had bone changes; the majority had lymphoblastic leukaemia. Only five cases have been recorded of bone lesions occurring in monocytic leukaemia (Windholz and Foster, 1949).

The changes observed radiologically fall into four groups:

1. *Osteolytic and destructive lesions.* Expansion of the marrow cavity by leukaemic proliferation leads to destruction of trabeculae, erosion and thinning of the cortical compact bone, and bone demineralization. This may be localized to one area of a long bone or generalized throughout it, and may be the cause of pathological fractures. The long bones are earliest affected, but later the process may involve the skull, vertebrae, ribs, mandible, and pelvis. Areas of bone erosion that were not demonstrable radiologically may be found at necropsy. The changes seen in radiographs therefore presumably represent lesions of some duration (Craver and Copeland, 1935).

2. *Periostitis.* Periosteal elevation with subperiosteal new bone formation is frequently associated with cortical erosion, and is due to leukaemic infiltration and subperiosteal osteoid formation. It may be multiple, causing the appearance of layering or stratification of the periosteum, and new bone may be formed at right angles to the shaft as well as parallel to it (Karshner, 1928; Lundholm,

1930; Connor, 1937). The metaphyseal ends of long bones are the sites most frequently involved, but the process may also involve the tubular bones of the hands and feet, and the ribs.

3. *Disordered epiphyseal growth.* Snelling and Brown (1935) and Baty and Vogt (1935) drew attention to a band of increased translucency frequently seen in the metaphysis of the long bones in cases of acute leukaemia. This band occurs most frequently at the sites of most rapid growth, i.e. at the distal ends of the femur, tibia, radius, and ulna. It may not extend completely across the bone, and can appear and disappear rapidly. It has since been described many times, and is by no means pathognomonic of leukaemia. It is similar to the 'Trümmerfeld zone' of scurvy, and has been found in syphilitic epiphysitis, congenital atresia of the bile-ducts, fibrocystic disease of the pancreas, chronic malnutrition, and other conditions of disordered growth. Baty and Vogt (1935) found it in 30 of their 43 patients, and Snelling and Brown (1935) in all of their 12 patients, in eight of whom it occurred without any other radiographic bone changes. It was found in 37 of 40 cases by Dale (1949) and in five of seven cases described by Gefferth (1941).

4. *Osteosclerosis* is a rare finding in the aleukaemic type of acute leukaemia in childhood, but is relatively common in chronic leukaemias with high white-cell counts in adults. It must be differentiated from Albers-Schönberg's disease, in which osteosclerosis is the primary lesion with a secondary leuco-erythroblastic anaemia.

Case Reports

Case 1. P. B., a boy of three years, was first noticed to have stiffness of the back on walking on November 23, 1948. A week later he complained of pain in both legs, and by December 20 he was unable to walk because of pain and rigidity in the spine and pain in both thighs. He was also noted to have become pale and to have lost his appetite. He was admitted to another hospital for investigation, and was there found to be anaemic and to have generalized lymphadenopathy. Bone changes were found radiologically in the lumbar spine and right femur. The white-cell count in the peripheral blood was 3,000 per c.mm., with 86 per cent. lymphocytes, and sternal puncture revealed a marrow picture consistent with the diagnosis of lymphatic leukaemia. He was transferred to the Hammersmith Hospital for aminopterin treatment on January 1, 1949. On admission he was a well-nourished child, with moderate pallor of the skin and mucosae. He could stand only with support. A few small mobile lymph-nodes were palpable in both supraclavicular regions, and the lumbar spine was held rigid, with some loss of the normal lordotic curve. There were no other abnormal signs on physical examination.

Investigations. The blood contained 4·6 million red cells per c.mm., haemoglobin 11·1 gm. per 100 ml., platelets 340,000 and white cells 5,800 per c.mm. (polymorphs 32 per cent., lymphocytes 63 per cent., monocytes 2 per cent., plasma-cells 3 per cent.). Marrow biopsy from the upper end of the tibia showed about 90 per cent. of the total cells to be of the lymphocyte series, mostly lymphoblasts, but with some differentiation to adult forms. The picture was that of a lymphoblastic leukaemia. On radiography the right humerus showed at its upper end a small area of bone destruction on the lateral side of the metaphysis, with disruption of the adjacent cortex and overlying periosteal

elevation. The appearance simulated a pathological fracture (Plate 30, Fig. 1 *a*). The upper ends of the femora were normal, but at the lower end of the right femur there was an area of dense calcification in the lateral part of the metaphysis, without periostitis (Plate 30, Fig. 2 *a*). The second lumbar vertebra was collapsed and wedged anteriorly; the other vertebrae were normal.

Progress. During the patient's second and third weeks in hospital he was given 8 mg. of aminopterin in doses of 1 mg. intramuscularly. This produced a moderately severe ulcerative stomatitis lasting a week; when it had healed, he developed a respiratory infection and left lower lobe pneumonia, for which he was treated with sulphamezathine. By the middle of February his chest was clear, and there was marked symptomatic improvement. His appetite returned, and he gained weight. The stiffness and pain in the spine had by this time disappeared, and he was able to walk unaided. Radiographs showed that the osteolytic and periosteal lesions at the upper ends of the humeri were no longer demonstrable, and the area of osteitis at the lower end of the right femur appeared to have resolved completely (Plate 30, Figs. 1 *b*, 2 *b*). X-rays showed no change in the state of the spine. The condition of the patient's blood and bone-marrow showed a reversion towards normal. The haemoglobin level had risen to 13·5 gm. per 100 ml., and platelets to 400,000 per c.mm. The white-cell count was 7,000 per c.mm. with 50 per cent. polymorphs and 42 per cent. adult lymphocytes. Tibial puncture on March 2 showed active leucopoiesis without positive evidence of leukaemia; blasts formed less than 1 per cent. of the total marrow-cells, and erythroblasts and granulocyte-precursors were present in normal proportions. He was sent home in apparently good general health on February 23. Two months later, although the child was still in good general health and with a normal blood picture, his tibial bone-marrow had relapsed; some 30 to 40 per cent. of the marrow-cells were of the lymphocyte series, about half being primitive blasts. A second course of 9 mg. of aminopterin was given early in May, with improvement in the marrow picture, but without complete eradication of the leukaemic cells. A radiographic survey at the end of May showed the bone architecture to be still normal at all the sites of previous infiltration. The child remained clinically well throughout the summer, although sternal marrow biopsies showed the persistence of leukaemia.

The patient's final admission was on August 29, 1949. At that time the bone-marrow had relapsed; the majority of the cells present were lymphoblasts, and granulopoiesis was minimal. The peripheral leucocyte count was still low (5,000 per c.mm.), but only 5 per cent. were polymorphs, and the remainder were lymphocytes of varying grades of immaturity. The haemoglobin and platelet levels had also begun to fall. A third course of aminopterin, totalling 12 mg., was given, but his condition declined very rapidly, without any clinical or haematological response to treatment, and he died on September 16. On the day of death the white-cell count fell to 750 per c.mm. Radiographs taken *post mortem* showed no abnormality of bone structure in the humeri or femora.

At autopsy (Dr. A. J. M. Reese) there was generalized enlargement of the lymph-nodes, and a moderate degree of leukaemic infiltration of the liver and kidneys. The long bones appeared normal to the naked eye, but the second lumbar vertebral body was compressed, and the compact cortical bone of most of the lumbar vertebral bodies appeared somewhat thinner than normal. The bone-marrow in the vertebrae, sternum, and all the long bones was deep red and gelatinous. On microscopic examination the bone-marrow was highly cellular and oedematous, with some evidence of erythropoiesis, but with considerable replacement by stem-cells and lymphocytes. A section was taken from the upper end of the right humerus. The periosteum at this site was moderately

thickened, but the cortical bone and articular cartilage were histologically normal. A slight degree of osteoclastic activity was present in some areas, but there was no evidence of active bone destruction or formation, and no invasion of the cortex or periosteum by leukaemic cells.

Case 2. B. W., a boy of seven years, previously well, developed malaise, pyrexia, and painful swellings of both elbow-joints early in November 1948, and during the next four weeks had migratory swellings of the elbows, knees, and ankles. He was pale and sweating, and required frequent analgesics. Rheumatic fever was diagnosed, and he was treated with salicylates, but the arthralgia and joint swellings persisted. On March 11, 1949, he was admitted to hospital with an abscess of the buttock; penicillin was given and the abscess was incised, but he continued febrile, and became increasingly anaemic. Examination of the blood and bone-marrow led to the diagnosis of acute lymphatic leukaemia, and on April 14 he was transferred to the Hammersmith Hospital for further treatment. On admission he was thin but not wasted, of good colour, and obviously in pain. His temperature was 99·4° F., and weight 42 lb. There was no purpura or external bleeding. His mouth and throat were healthy. Small mobile lymph-nodes were palpable in the neck, axillae, groins, and epitrochlear regions. The salivary glands were not enlarged, and the liver and spleen were not palpable. The cardiovascular system and lungs were normal. Movements of the left shoulder and elbow were restricted, and on palpation the upper third of the left humerus was thickened and tender over its lateral aspect. The left knee was slightly swollen and tender, with a small effusion into the joint. There was marked wasting of the quadriceps, and the lower end of the femoral shaft was tender on deep pressure. The other bones and joints were clinically normal.

Investigations. The red blood-cells were 4·2 million per c.mm., haemoglobin 13·5 gm. per 100 ml., platelets 70,000 per c.mm., and white cells 2,500 per c.mm. (polymorphs 5 per cent., lymphocytes 86 per cent., lymphoblasts 8 per cent., and monocytes 1 per cent.). Biopsy from a sternal puncture showed a highly cellular bone-marrow; the majority of the cells were small, atypical primitive forms, vacuolated and with scanty cytoplasm, and were considered to be lymphoblasts. On radiography the chest, skull, right humerus, hands, femora, and knees appeared normal. There was considerable elevation of the periosteum of the left humerus, extending from the upper end almost the whole length of the shaft. In addition there were multiple osteolytic areas in the cortex of the upper third, giving the bone a worm-eaten appearance (Plate 31, Fig. 3 *a*). The body of the ninth dorsal vertebra showed a slight degree of wedging, but the bone structure was not radiologically abnormal.

Progress. For the first week the patient was febrile, and had constant severe pain in the left knee and arm, necessitating the frequent administration of pethidine. Aminopterin was then given, in daily doses of 1 mg. by mouth, for 13 days. The bone pains ceased after three doses, and by the tenth day of treatment the effusion in the left knee had been absorbed, and the affected joints were all painless and fully mobile. Treatment was complicated by a severe haemorrhagic stomatitis, and the resulting fall of the haemoglobin to 4·5 gm. per 100 ml. necessitated a blood transfusion. After this the patient became afebrile, and a general improvement began which was maintained until his discharge. His appetite returned, and his weight increased. After a severe leucopenic phase, maximal on the seventh day after aminopterin was discontinued, his peripheral blood count reverted to normal, and sternal puncture on June 9 showed that only 6 per cent. of the cells were lymphoblasts, and

developing granulocytes and erythroblasts were present in normal proportions. Radiographs of the long bones on May 26 showed subperiosteal new bone formation in the left humerus, with healing and slight sclerosis of the cortex. The femora were both normal. A second course of 8 mg. aminopterin was given in June, and when he was sent home on June 28 the child was walking well, had no palpable enlargement of the glands or spleen, and no bone tenderness or joint symptoms. Radiographs showed that the periosteal and cortical changes in the left humerus had largely resolved, but there was now a wide line of increased density immediately distal to the epiphysis at the upper end (Plate 31, Fig. 3 *b*). A similar line was present in the right humerus, but the bone was otherwise normal. On the lateral aspects of both femora at the upper ends, immediately adjacent to the growth cartilages, an incomplete band of increased translucency was demonstrable, but no other bone changes were seen.

On August 9 the patient was readmitted complaining of pain in the back of two weeks' duration. There was pronounced rigidity of the dorsi-lumbar spine, with spasm of the erector spinae muscles, but all the other bones and joints were clinically normal. There was no enlargement of lymph-nodes, and the liver and spleen were not palpable. The haemoglobin was 13·8 gm. per 100 ml., and the white blood-cells 7,000 per c.mm. (polymorphs 18 per cent., lymphocytes 74 per cent., lymphoblasts 8 per cent.). Sternal puncture confirmed a relapse in the leukaemic process. Bone radiographs showed collapse of many of the dorsal and lumbar vertebral bodies (Plate 33, Fig. 5). There was no change in the radiographic appearance of the humeri or femora. During the next month he was given two further courses of aminopterin, without any sustained improvement in the condition of his blood or bone-marrow. He continued aleukaemic, with increasing anaemia and thrombocytopenia. He had intermittent backache, forward angulation of the spine in the lower dorsal and upper lumbar region, and pain in the right elbow with restricted movement but without effusion or peri-articular swelling. The radiographic appearance of the left humerus on October 13 was unchanged, but the right humerus had an appreciable degree of periosteal elevation, involving the upper two-thirds of the shaft (Plate 32, Fig. 4 *a*). In spite of a fifth course of aminopterin and a course of 20 mg. of amethopterin, his condition rapidly deteriorated. The leucocytes rose to 63,000 per c.mm., 80 per cent. being lymphoblasts. The patient died on November 10 with haematemesis, rectal bleeding, and generalized purpura. Radiographs taken *post mortem* showed no bony abnormality in the femora, tibiae, or fibulae. There was collapse with anterior wedging of practically all the dorsal and lumbar vertebrae, but the disc spaces were preserved. The areas of osteolysis in the shaft of the left humerus had healed, and there was some residual cortical sclerosis. The periosteal elevation previously noted in the right humerus was less marked, and juxta-epiphyseal bands were present at the heads of both humeri, that on the left being incomplete (Plate 31, Fig. 3 *c*; Plate 32, Fig. 4 *b*).

At autopsy (Dr. A. J. M. Reese) there was generalized enlargement of the lymphoid tissue, and leukaemic infiltration of the heart, pericardium, pleurae, lungs, spleen, liver, and kidneys. The immediate cause of death was massive haemorrhage into the stomach and intestine. The vertebrae were collapsed and filled with greyish-red marrow; the marrow of the long bones was red and gelatinous. The periosteum over the upper half of the left humeral shaft was visibly thickened, but the bone appeared otherwise normal. The synovial membrane in the left knee appeared normal to the naked eye. Histologically, sections of the bone-marrow showed greatly increased cellularity and uniform replacement with primitive leukaemic cells. Granulocytes were very incon-

spicuous. Longitudinal and transverse sections of the upper end of the left humerus showed a dense layer of leukaemic cells beneath the thickened periosteum, with chains of cells growing out into the periosteum itself (Plate 34, Fig. 8). There were no signs of abnormally increased new bone formation or of osteoclasis. The compact cortical bone showed spaces filled with masses of leukaemic cells, but there was no demonstrable difference between the area immediately proximal to the epiphyseal cartilage and the rest of the section. The synovial membrane of the left knee was histologically normal.

Case 3. L. H., a boy aged four and a half years, had a febrile illness with tonsillitis, parotitis, and enlarged cervical glands in April 1949, and although the throat infection and parotid swelling resolved he became increasingly pale, anorexic, and weak. He was therefore admitted to another hospital for investigation on May 4. He was noted to be febrile and anaemic, and had enlargement of all the salivary glands, and of the lymph-nodes, liver, and spleen. Enlarged mediastinal glands were causing some respiratory obstruction. A diagnosis of acute leukaemia was made after marrow biopsy; he was given a blood transfusion, and was sent home on May 30. His condition then rapidly deteriorated, and he developed ascites and oedema of the lower limbs. He was admitted to the Hammersmith Hospital on June 20 for treatment with aminopterin. On admission he was a pale, wasted, and dyspnoeic child. His temperature was 101° F. There were bruises on the trunk and legs, and dependent oedema of the genitalia and lower limbs. The superficial lymph-nodes in all regions were greatly enlarged, and there was bilateral swelling of the parotid and submandibular salivary glands. The abdomen was distended with fluid, but the liver could be palpated 2 cm., and the spleen 5 cm., below the costal margin; a central hard mass was present and was thought to be enlarged mesenteric glands. Apart from a hyperkinetic circulation there were no other abnormal physical signs.

Investigations. The red blood-cells were 1·2 million per c.mm., haemoglobin 3·7 gm. per 100 ml., and reticulocytes 15 per cent. The platelets were 180,000 per c.mm., and white cells 49,000 per c.mm. (blast cells 14 per cent., myelocytes 2 per cent., metamyelocytes 11 per cent., polymorphs 21 per cent., lymphocytes 50 per cent., and monocytes 2 per cent.). Many of the lymphocytes were immature, and there were 114 nucleated red cells at all stages of development per 100 white cells. Marrow biopsy showed active erythropoiesis, but little evidence of granulopoiesis. The majority of the cells present were small nucleolated lymphoblasts. On radiography of the skeleton, the chest appeared normal; there were areas of cortical bone destruction at the surgical necks of both humeri, without new bone formation or periosteal elevation (Plate 33, Fig. 6 *a*) and a similar appearance at the lower end of both ulnae. The knees showed periosteal elevation at the distal ends of the femoral shafts, with multiple small areas of cortical destruction in the right medial femoral condyle, and on the medial side of the proximal end of the left tibial diaphysis. The spine and the rest of the skeleton were normal.

Progress. A blood transfusion given on June 22 raised the haemoglobin to 14·1 gm. per 100 ml. Six daily doses of 1 mg. aminopterin were given by mouth from June 27 to July 2. At the end of the treatment the glandular masses were all appreciably smaller, and a week later the lymph-nodes, liver, and spleen could no longer be felt, the abdomen was no longer distended, and the oedema of the lower limbs had disappeared. The white-cell count fell precipitously during treatment, and four days after the last dose of aminopterin it was 700 per c.mm. At this stage he developed severe vomiting, haemorrhagic stomatitis,

and bleeding from puncture sites, and rapidly became dehydrated and exsanguinated. The child's condition became grave. Procaine-penicillin was administered parenterally, and a second transfusion given. Dehydration was countered by a continuous rectal drip of glucose saline. His condition then began to improve, and from July 11 progress was rapid. The extensive buccal stomatitis and pharyngitis, which had become secondarily infected, healed, and he gained weight and strength. The white-cell count, haemoglobin, and platelets increased to normal levels, and when he was discharged on July 21 the patient was afebrile and appeared well, with no abnormal physical signs. The white cells were 6,000 per c.mm., with 85 per cent. mature polymorphs, 11 per cent. adult lymphocytes, and no primitive cells. His haemoglobin was 13·6 gm. per 100 ml., and platelets 600,000 per c.mm. The bone-marrow had completely changed. The few lymphocytes present were all adult forms, erythropoiesis was normal, and granulopoiesis was prominent, metamyelocytes being the dominant cells. The patient was readmitted for three days on August 18, 1949, because of a bilateral facial nerve palsy of lower motor neurone type. His blood count was still normal, and he was otherwise well. A radiographic survey of the skeleton showed the lesions in the necks of the humeri to have resolved, and the cortex of the bone was intact and clearly defined (Plate 33, Fig. 6 *b*). The lesions at the lower ends of the ulnae and around the knees were no longer demonstrable, and the bone at these sites was radiologically normal.

One month later the child was admitted for the third time. He had had anorexia, loss of energy, and rapidly enlarging cervical lymph-glands for one week. The right facial nerve palsy was now almost gone, and that on the left had improved; but there was generalized lymphadenopathy, and the spleen was again palpable. The haemoglobin level had risen spontaneously to 15·5 gm. per 100 ml., and the platelets were 270,000 per c.mm., but there was a leucocytosis of 33,000 per c.mm. in the peripheral blood, of which some 5 per cent. were lymphoblasts. The sternal marrow showed clear evidence of a relapse in the leukaemic process. A further 8·5 mg. of aminopterin was given over the next four weeks, with little sustained improvement. He became febrile, and his general state deteriorated, while the peripheral blood and bone-marrow became more frankly leukaemic. He was sent home on October 25, and died there a month later. Autopsy was not obtained.

Case 4. J. D., a girl aged five and a half years, was first noticed to be unusually pale in December 1948, but pallor did not become marked until after an attack of bronchitis early in January 1949, when she developed increasing fatigue, night sweats, and failure to thrive. She was admitted to another hospital on February 1, 1949, and was found to be severely anaemic, with enlargement of the spleen and superficial lymph-nodes. The white-cell count was 4,200 per c.mm., with a preponderance of lymphocytes, and a bone-marrow biopsy suggested the diagnosis of lymphatic leukaemia. During April her condition deteriorated; anaemia and lymphadenopathy increased, and both parotid glands became enlarged. She was transferred for treatment on April 29. On admission she was a thin, pale child, with petechial haemorrhages in the buccal mucosa and ecchymoses on both arms; her temperature was 102° F. Small, firm glands were palpable in the neck, axillae, and groins. The parotid and submandibular salivary glands were enlarged and tender. The spleen and liver were found to be enlarged on palpation. No other abnormalities were found on physical examination.

Investigations. The red blood-cells were 2·0 million per c.mm., haemoglobin 7·4 gm. per 100 ml., platelets 46,000 per c.mm., and white cells 2,700 per c.mm.

(polymorphs 32 per cent., lymphocytes 64 per cent., monocytes 4 per cent.). Marrow biopsy from the iliac crest showed about 75 per cent. of the marrow cells to be of the lymphocyte series; most were nucleolated blast cells, but a few adult forms were present. The appearance was that of lymphoblastic leukaemia. On radiography there was a small area of cortical bone destruction at the distal end of the left tibia, chiefly on the lateral aspect, and periosteal elevation over the antero-medial aspect of the bone. The periosteum at the proximal end of the left first metatarsal was also slightly elevated. The rest of the skeleton, including the spine, was radiologically normal.

Progress. A transfusion of 570 ml. of blood given on May 5 raised the haemoglobin to 9·7 gm. per 100 ml. Aminopterin in oral doses of 1 mg. was commenced on May 10, and treatment was completed on June 1, 15 mg. having been given. Clinical improvement was noticed after 6 mg. had been given. The child became afebrile, her appetite improved, and she commenced to walk, but limped slightly on the left foot. At the end of treatment a few small glands were felt in the neck only, and the salivary glands, liver, and spleen were no longer palpable. Her weight had increased, and her colour had improved. Radiographs showed no further progress in the bone lesions. The aminopterin therapy had no apparent effect on the peripheral blood; the white-cell count remained at 4,000 to 8,000 per c.mm., with 20 to 30 per cent. polymorphs and 50 to 60 per cent. mature lymphocytes. Iliac crest puncture on June 9, however, showed a great reduction in the leukaemic process in the marrow. About half the cells were lymphocytes, but only 1 per cent. were as primitive as those seen before treatment, and normally developing granulocytes and erythroblasts were numerous. She was sent home on June 16 in good general condition.

When seen a month later the patient was still well, and had gained 4½ lb. in weight. Her haemoglobin had risen to 15·8 gm. per 100 ml., and the total and differential leucocyte counts were normal. She complained, however, of occasional backache, and a radiograph of the spine showed that the bodies of the seventh, ninth, and twelfth dorsal vertebrae were wedged anteriorly and the second lumbar vertebra was vertically compressed (Plate 33, Fig. 7). She walked normally. At the end of August 1949 it became obvious that she was relapsing; her weight and haemoglobin level began to fall, and she became anorexic and listless. The liver and spleen again became palpable, and the bone-marrow showed a marked increase in the number of lymphoblasts. A second course of 7 mg. of aminopterin was given from September 12 to 18, after which 0·25 mg. was given on alternate days. There was a satisfactory response to treatment; the visceral enlargement regressed, she regained her lost weight and energy, her haemoglobin rose spontaneously to 17·2 gm. per 100 ml., and there was a decrease in the number of leukaemic cells in the bone-marrow. The backache subsided soon after the course of aminopterin was completed, and radiographs of the left foot showed that the lesions previously demonstrated had healed. The radiographic appearances in the spine were unaltered. This remission lasted just under three months. In the middle of December the patient's condition rapidly deteriorated clinically and haematologically, in spite of an increase in the dose of aminopterin to 0·25 mg. daily, and she died on December 26, 1949, with hyperpyrexia.

At autopsy (Dr. I. Doniach) the gastro-intestinal tract, lungs, heart, brain, and endocrine glands showed no significant abnormality. The liver and kidneys were not enlarged, and appeared normal on section. The spleen was slightly enlarged but of normal pattern. There was slight enlargement of the cervical, abdominal, and iliac groups of lymph-nodes, and of the submaxillary glands. The bone-marrow in the sternum and vertebrae was pink; the long bones contained a

mixture of red gelatinous and yellow fatty marrow throughout. Apart from compression of the ninth dorsal vertebral body, the bones and joints appeared normal to the naked eye. Microscopically, there was a complete absence of leukaemic infiltration of any of the solid viscera, or of the heart, gastro-intestinal tract, lungs, or endocrine glands. The submaxillary glands showed a very slight excess of lymphocytes in the interstitial tissue between the acini. The lymph-nodes generally were abnormally empty of cells, and many of the surviving lymphocytes had karyorrhectic nuclei. The sternal bone-marrow was largely depleted of cells, the stroma being filled with albuminous material with areas of haemorrhage. There were scattered islands of residual cellularity showing normoblastic erythropoiesis and granulopoiesis, a few megakaryocytes, and a slight excess of lymphocytes and primitive blast cells. The marrow in the vertebrae and long bones had a similar appearance. The structure of the first dorsal vertebra was normal, but the ninth was vertically compressed without any signs of bone destruction or of leukaemic infiltration. The first left metatarsal showed, at its lower end, old periosteal proliferation and subperiosteal infiltration with lymphocytes, which had invaded the periosteum and were lying in chains between the fibres (compare Plate 34, Fig. 8, and Plate 35, Fig. 10). The articular and epiphyseal cartilages appeared normal; the cortical bone was intact, and there was no new bone-formation.

Case 5. K. T., a boy of 15 years, had had rheumatic fever at the age of five, from which he recovered completely. In November 1948 he had had a very severe attack of erythema multiforme exudativum with bullous skin lesions, oropharyngitis, and ophthalmia, and was gravely ill. At the height of the illness the white-cell count was 46,000 per c.mm., with 92 per cent. of mature polymorphs, and as he improved it gradually fell to normal. By August 1949 he had recovered, and had started work as an apprentice electrician. The leucocyte count at that time was 8,000 per c.mm., with a normal distribution of white cells. Towards the end of October he began to tire easily, and complained of stiffness of the joints. He was found to be anaemic (haemoglobin 7·1 gm. per 100 ml.), and his spleen was palpable. The leucocytes were 56,000 per c.mm., with 22 per cent. granulocyte-precursors, mostly myelocytes. A sternal biopsy was suggestive of myeloblastic leukaemia. He rapidly lost weight and became more anaemic. On November 1, 1949, he was transferred to the Hammersmith Hospital for treatment. On admission he was found to be pale and dyspnoeic, and the circulation was hyperkinetic. There was extensive scarring of the skin over his right elbow, neck, right ear, iliac crests, and right knee and leg, residua of his erythema multiforme exudativum. The pharynx, mouth, and gums were healthy, and there was no purpura. The superficial lymph-nodes, spleen, and liver were palpable and moderately enlarged.

Investigations. The red blood-cells were 0·63 million per c.mm., haemoglobin 3·4 gm. per 100 ml., platelets 45,000 per c.mm., and white cells 178,000 per c.mm. (blast cells 17 per cent., promyelocytes 5 per cent., neutrophil myelocytes 13 per cent., metamyelocytes 19 per cent., polymorphs 39 per cent., lymphocytes 7 per cent.). Marrow biopsy from the sternum revealed a highly cellular marrow containing numerous peroxidase-negative myeloblasts, but there was a good deal of differentiation to adult polymorphs, indicating a subacute type of myeloblastic leukaemia. Erythropoiesis was normoblastic in type, and few megakaryocytes were present.

Progress. Transfusions of packed red cells, given during his first week in hospital, raised the patient's haemoglobin to 9·0 gm. per 100 ml. Treatment by generalized irradiation with small daily doses of X-rays was commenced on

November 8. On the following day he developed pain and swelling in the joints of the fingers and in the knees. Examination showed tenderness and effusion in the left third and right fifth metacarpophalangeal joints, and in both knees. Radiographs of the hands, knees, and legs were normal. Synovial fluid aspirated from the left knee-joint was normal in colour and moderately viscous. Its protein and sugar contents were normal (4·2 gm. and 89 mg. per 100 ml. respectively). The leucocytes in the fluid numbered 2,700 per c.mm., 50 per cent. being polymorphs, about 10 per cent. lymphocytes, and the remainder mononuclear cells having the appearance of granulocytes. Soon afterwards he developed, in addition, a painful restriction of movement in the left elbow and ankle, but 10 days after the onset of articular symptoms all the effusions had resolved and the joints were painless and fully mobile. X-ray treatment was continued for one month. At the end of that time the liver and spleen were no longer palpable, and the white blood-cells had been reduced to 63,000 per c.mm. There was no change in the differential count, and the appearance of the bone-marrow was unaltered. During the period of treatment the patient's haemoglobin continued to fall, and further transfusions were required. By the end of December the white-cell count had risen again to 200,000 per c.mm., mainly immature granulocytes. The spleen, liver, and lymph-nodes were again palpable, and he was purpuric. He complained of pains in the hands, feet, and elbows, and was found to have effusions in the right third metacarpophalangeal and left fourth proximal interphalangeal joints. Both ankles were restricted in movement, tender, and painful. Radiographs of the limbs showed changes only in the right ankle and right hand; there was a moderate periosteal elevation over the distal end of the right fibular shaft and at the base of the third right metacarpal. Treatment by amethopterin, in daily oral doses of 2·5 mg., was commenced on December 30, but was discontinued on January 9, 1950, owing to the development of bilateral nerve deafness. The white-cell count was unchanged, but the spleen and liver were smaller, and the joint effusions had subsided rapidly after treatment had begun. On the following day the patient suddenly lapsed into coma and died of an intracerebral haemorrhage.

At autopsy (Dr. I. Doniach) there were scattered petechial haemorrhages on the limbs and trunk. The cause of death was a massive haemorrhage at the base of the brain, involving the right cerebellar hemisphere and midbrain. The pericardial surface of the left ventricle and the mucosa of the stomach were covered with petechial haemorrhages. The liver was considerably enlarged, pale, and smooth. The spleen was enlarged and soft, but of a normal pattern. The kidneys were not enlarged, and showed no naked-eye abnormality. The lymph-nodes generally were enlarged and firm. The rest of the viscera, endocrine glands, and alimentary tract appeared normal. The sternal bone-marrow was bright red, and the long bones contained red marrow throughout. The metacarpal bones, metacarpophalangeal joints, and right fibula and ankle-joint appeared normal to the naked eye. The synovial membrane of the knees was slightly thickened, but otherwise normal. On histological examination the small vessels throughout the body were full of leucocytes, and there was widespread invasion of the tissues by leukaemic cells. The pericardium, heart, lungs, stomach, liver, kidneys, spleen, lymph-nodes, and testes all showed varying degrees of infiltration. Bone-marrow from the sternum, long bones, and metacarpals was highly cellular; the majority of the cells were leukaemic and of primitive type, but there was some degree of differentiation to adult granulocytes, and normoblastic erythropoiesis was demonstrated. Megakaryocytes were scanty. A section of synovial membrane from the right knee was densely infiltrated with large primitive cells, many being in mitosis (Plate 34, Fig. 9).

The right third metacarpophalangeal joint was microscopically normal, but the periosteum at the base of the metacarpal was about twice the normal width. A section from the lower end of the diaphysis of the right fibula showed proliferation and infiltration of the periosteum, and a wide zone of lymphocytes separating it from the cortex of the bone. There was clear evidence of the laying down of new subperiosteal bone in this area (Plate 35, Figs. 10, 11).

Discussion

The use of folic acid antagonists in acute leukaemia arises from the observation that the administration of pteroylglutamic acid or its conjugates apparently intensifies the leukaemic process (Farber, Cutler, Hawkings, Harrison, Peirce, and Lenz, 1947). When, therefore, synthetic compounds biologically antagonistic to folic acid were prepared, they were applied in the treatment of leukaemia. Meyer (1948) obtained temporary clinical and haematological remissions in four out of five patients with acute leukaemia treated with pteroylaspartic acid and methylpteroic acid, and in the same year Farber, Diamond, Mercer, Sylvester, and Wolff (1948) reported significant remissions in 10 out of 16 children treated with aminopterin. In a later report Farber (1949) summarized data referring to 60 children with acute leukaemia treated with aminopterin and other folic acid antagonists. Clinical and haematological remissions were obtained in 50 per cent. of these patients, and in two cases were maintained for 16 and 23 months respectively. The reported incidence of remissions in cases treated by other authors varies from 11 per cent. (Meyer, Fink, Sawitsky, Rowen, and Ritz, 1949) to 45 per cent. (Peirce and Alt, 1948). Dacie, Dresner, Mollin, and White (1950), in a study of 13 patients, including Cases 1, 2, and 4 of the present series, found that remissions were induced in nine. Seven of the patients were children and all showed a significant response of varying duration, the maximum period of remission being about nine months. Only two of the six adults had remissions, and then only for four to six weeks. The lymphoblastic type of leukaemia appeared to be the most responsive. In cases of response to anti-folic acid compounds immature cells usually disappear from the peripheral blood, and leukaemic tissue in the bone-marrow is replaced by normally developing erythrocytes and granulocytes. The number of leukaemic cells in the marrow may be reduced to one per cent., but they have not been observed to be entirely eradicated. Concurrently there is a spontaneous rise in the levels of haemoglobin and platelets, and clinical improvement occurs which is characterized by a gain in weight, a regression in size of the enlarged lymph-nodes, spleen, and liver, and a return of the patient to normal activity.

The first four patients reported in the present paper had aleukaemic lymphoblastic leukaemia, and all responded well, haematologically and clinically, to their initial course of treatment. There was in every case a considerable reduction of the leukaemic process in the bone-marrow, which reverted almost to normal, and this coincided with a clinical remission which was most striking in Case 3. The effect of the anti-folic acid agents in relieving osteo-articular symptoms was impressive, and preceded the reversal of the bone lesions which was found

in all these patients by radiography. The leukaemia in Case 5 was myeloblastic in type, and amethopterin was given only towards the end, when X-ray therapy had failed to control the disease. In this case, although joint symptoms were severe, radiological changes were slight, and neither these nor the blood were altered by the relatively small amounts of amethopterin given. The remissions induced by folic acid antagonists are, at best, only temporary, and it was to be anticipated that subsequent relapses might be followed by a recurrence of the bone lesions. This did in fact occur in Case 2, and in the three patients in whom the spine was involved the lesion appeared to be progressive during the remission. It is clear, too, that the disappearance of radiological lesions does not necessarily imply complete healing. In Case 2 the left humerus was radiologically normal at death, but histological examination showed considerable subperiosteal leukaemic infiltration, and a similar condition was found in the radiologically healed metatarsal of Case 4. Radiologically visible changes must therefore be taken as representing fairly advanced lesions, and their absence cannot be interpreted as evidence that the bone is normal. In other patients, in whom bone pains and arthralgia have been a severe and distressing feature of the disease, we have found radiographs to be consistently negative. In these cases the fact that folic acid antagonists improved the blood picture and relieved the bone pains indicated their leukaemic origin.

Leukaemic infiltration of bone appears to bear no relation to leukaemic infiltration elsewhere in the body. This was especially noticeable in Case 4 in which, at autopsy, there was no infiltration of any other organ, and the bone-marrow and lymphoid tissue were hypoplastic. Little has been written about the pathology of the joint lesions in leukaemia. Conybeare (1936) and Wintrobe and Mitchell (1940) reported no significant change in the affected joints at autopsy, and Bichel (1948) stated that there are usually no inflammatory signs in joints examined *post mortem*, even when clinically inflamed. In Case 5 leukaemic cells were demonstrated in the synovial fluid from the inflamed knee, and at autopsy eight weeks later the synovium was found to be extensively infiltrated by leukaemic deposits. Such leukaemic synovitis is presumably responsible for many of the joint symptoms of leukaemia.

I wish to thank Dr. D. MacCarthy and Dr. D. H. Garrow, under whose care the patients were admitted, for permission to publish the case reports. I should also like to thank Dr. J. Duncan White for permission to use the radiographs, and Dr. J. C. White for performing the marrow biopsies.

Summary

The clinical, radiographic, and histological aspects of the bone and joint lesions seen in five cases of acute leukaemia in children are described. During temporary remissions of the leukaemic process, induced by the folic acid antagonist aminopterin, a reversal of these lesions was demonstrated clinically and radiographically.

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FIG. 1*a*. Case 1. Localized area of osteolysis with overlying periosteal elevation in the proximal humeral metaphysis.

FIG. 1*b*. Case 1. The right humerus after treatment with aminopterin. Bone now radiologically normal.

FIG. 2*a*. Case 1. Localized area of calcification in lateral part of metaphysis of right femur. No periostitis.

FIG. 2*b*. Case 1. Right femur after aminopterin. Bone radiologically normal.

FIG. 3*a*. Case 2. Left humerus before treatment. Extensive cortical bone destruction and periosteal elevation.

FIG. 3*b*. Case 2. Resolution of periosteal elevation and cortical destruction after aminopterin therapy. A broad line of increased density is present immediately adjacent to the epiphyseal cartilage.

FIG. 3*c*. Case 2. Left humerus. Post mortem specimen, showing slight residual cortical sclerosis. A band of increased translucency is present distal to the lateral half of the epiphyseal cartilage.

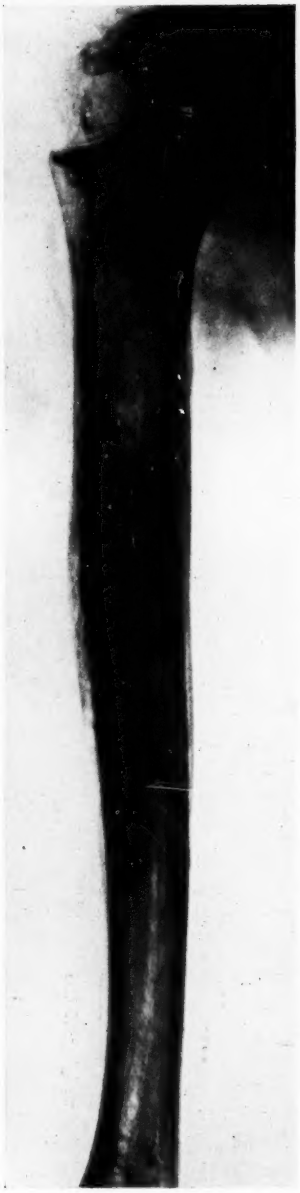

FIG. 4*a*. Case 2. Leukaemic relapse after aminopterin. The periosteum over the shaft of the humerus is greatly thickened and there is an osteolytic focus in the upper third of the bone.

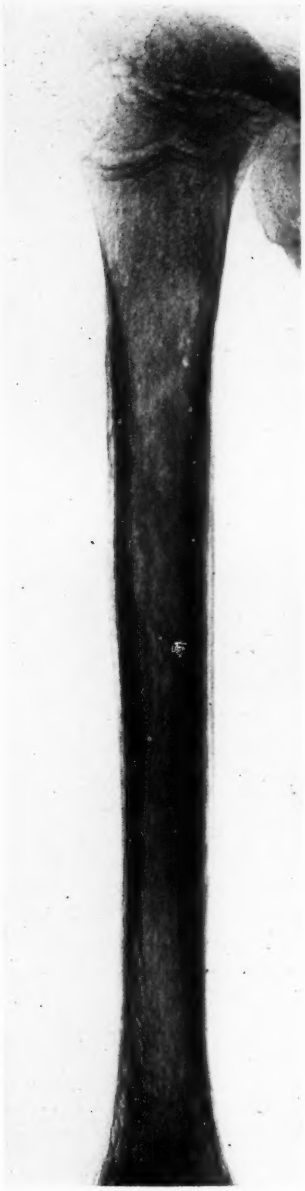

FIG. 4*b*. Case 2. Right humerus. Post mortem specimen. Periostitis much less marked. There is a band of increased translucency below the epiphysis.

FIG. 5. Case 2. Collapse and anterior wedging of the thoracic vertebrae.

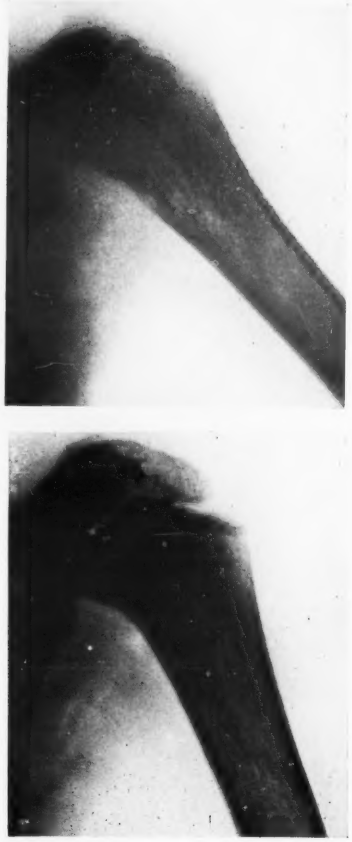

FIG. 6. Case 3. Neck of humerus, showing (*a*) cortical destruction, (*b*) healing after aminopterin.

FIG. 7. Case 4. Collapse of dorsal and lumbar vertebral bodies.

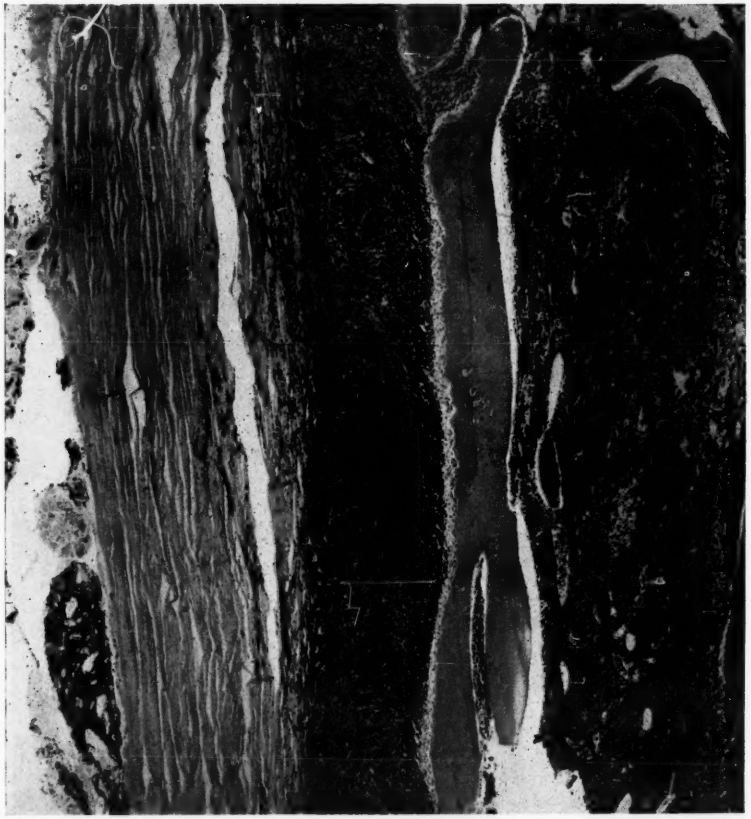

FIG. 8. Case 2. Section from the proximal metaphysis of the left humerus, showing the thickened and infiltrated periosteum on the left and the dense subperiosteal leukaemic infiltration (haematoxylin and eosin, ×42).

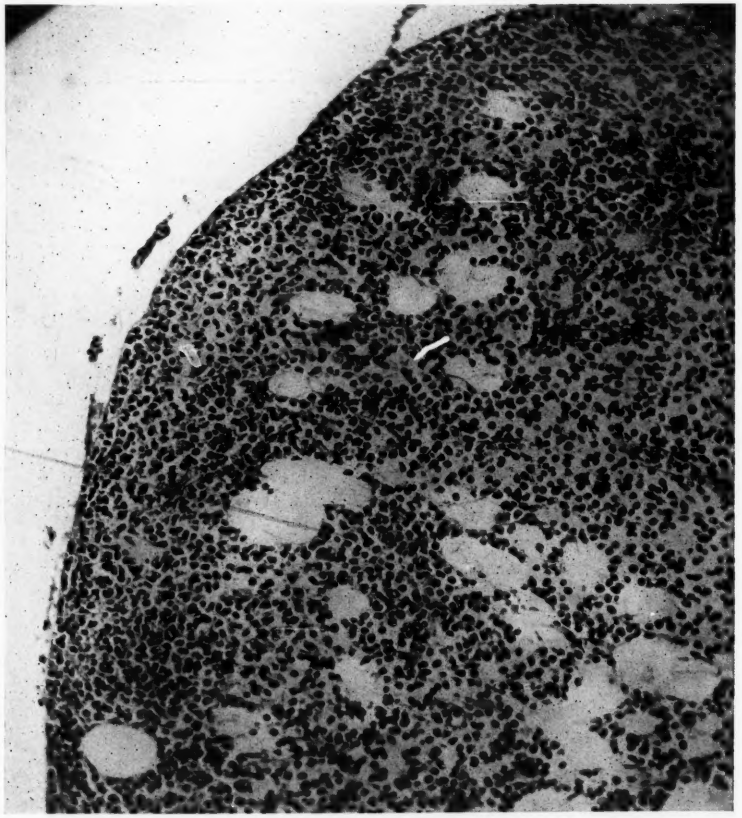

FIG. 9. Case 5. Section of synovial membrane from the knee, showing dense leukaemic infiltration (haematoxylin and eosin, ×150).

FIG. 10. Case 5. Low-power view of section from the lower end of the fibula. The periosteum (on the left) is thickened and infiltrated with leukaemic cells, which constitute a broad layer between it and the thinned cortical bone on the right. Osteogenic fibres can be seen passing from the deeper layers of the periosteum to the cortex (haematoxylin and eosin, × 75).

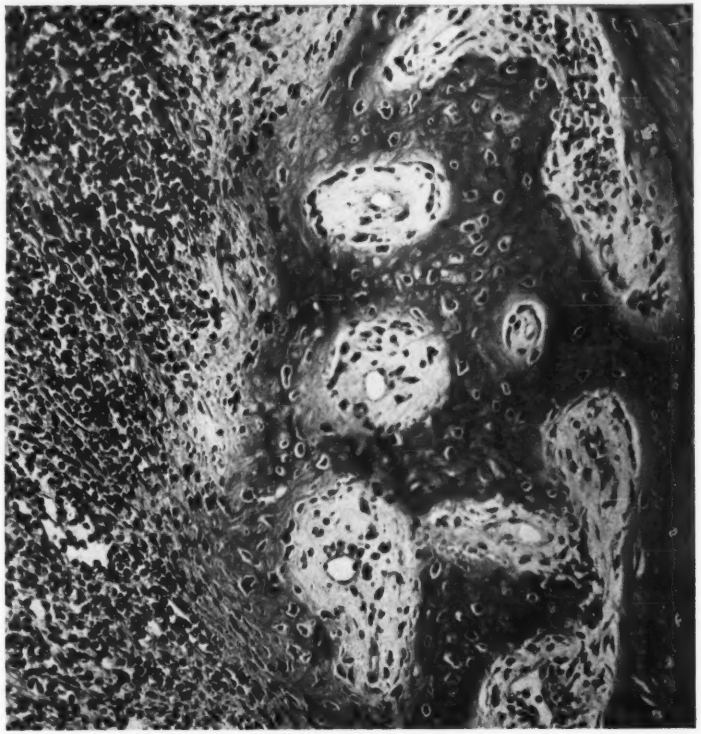

FIG. 11. Case 5. High-power view from the section shown in Fig. 10, showing subperiosteal new bone formation (haematoxylin and eosin, × 145).

THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1950

FORTY-FOURTH ANNUAL GENERAL MEETING

THE FORTY-FOURTH ANNUAL GENERAL MEETING was held in London on Friday and Saturday, May 26 and 27, 1950, in the William Beveridge Hall, Senate House, University of London. The attendance book was signed by 220 members and 18 visitors. The proceedings began at 10.10 a.m.

The President, Professor Sir William Thomson, was in the Chair.

The Minutes of the last Annual General Meeting having been published in the *Quarterly Journal of Medicine* were taken as read, confirmed, and signed.

Election of Officers

President. Sir John Parkinson was elected President and took the Chair. He expressed the thanks of the Association to the retiring President, Professor Sir William Thomson.

The election of the Executive Committee, Honorary Members, Extra-Ordinary Members, and Ordinary Members then followed.

Executive Committee

President. Sir John Parkinson.

Treasurer. Dr. C. Newman.

Secretary. Dr. W. I. Card.

Members for England:

Dr. G. Bourne.
Dr. T. C. Hunt.
Professor R. E. Tunbridge.
Dr. K. Shirley Smith.
Dr. A. M. Cooke.
Professor R. Platt.

Members for Scotland:

Dr. J. K. Slater.
Dr. W. R. Snodgrass.
Professor H. W. Fullerton.

Members for Ireland:

Dr. A. Thompson.
Dr. H. Hilton Stewart.
Dr. F. F. Kane.

Election of Honorary Member

Professor Sir William Thomson.

Election of Extra-Ordinary Members

Dr. Hugh Barber.
Professor J. W. McNee.
Dr. A. G. Maitland-Jones.
Sir Edward Mellanby.
Professor H. F. Moore.
Dr. J. K. Rennie.
Dr. J. A. Smyth.
Professor Sir James Spence.

Election of Editor

Dr. A. M. Cooke.

Election of Ordinary Members

Kenneth Oscar Black, M.D., F.R.C.P., Assistant Physician, St. Bartholomew's Hospital, London.

Jonas Henrik Kellgren, M.B., M.R.C.P., F.R.C.S., Director, Nuffield Department of Rheumatic Diseases, Manchester.

George Durant Kersley, M.D., F.R.C.P., Director, Research Unit, Royal National Hospital for Rheumatic Diseases, Bath.

Jack Watson Litchfield, M.B., F.R.C.P., Assistant Physician, St. Mary's Hospital, London.

Clifford Gregory Parsons, M.D., F.R.C.P., Physician, Birmingham United Hospitals.

William Phillips, M.D., F.R.C.P., Physician, United Cardiff Hospitals.

James Reid, M.D., M.R.C.P., Lecturer in Medicine, University of Glasgow.

John Samuel Richardson, M.V.O., M.D., F.R.C.P., Physician to Out-patients, St. Thomas's Hospital, London.

Charles Kelman Robertson, M.D., F.R.C.P.E., Assistant Physician, Royal Infirmary, Edinburgh.

Place of Meeting in 1951. Professor J. W. McNee formally invited the Association to meet at Glasgow at Whitsuntide in 1951.

The Treasurer presented the Annual Accounts for 1949–50. He pointed out that as the year started with a balance of £462 and finished with a balance of £539, the Association was solvent, though not saving money to a desirable extent on a total subscription income of £660 per annum. The amount on the Capital Account had increased from £3,130 to £3,247, and there was therefore money available for any emergency purposes. Until the question of a policy with regard to expenditure on the *Journal* had been considered, he was not suggesting a rise in the subscription rate. The Accounts were approved and adopted.

The Secretary asked for an Amendment to Rule 15. With the present delays in printing, six weeks was an inadequate time before the Annual Meeting for the submission of proposals for election. On the proposal of DR. NEWMAN, seconded by SIR WILLIAM THOMSON, it was agreed to amend Rule 15 by deleting 'six' and inserting 'ten'. The Secretary also asked for consideration of a proposal that all degrees and diplomas be omitted from the printed list of Members, which should contain only their names, titles, and addresses. After some discussion the proposal was carried *nem. con.*

PROFESSOR R. E. TUNBRIDGE asked permission to move the following resolutions: (1) That a Travelling Club be formed under the aegis of the Association of Physicians. (2) That any member of the Association shall be eligible to participate in the activities of the Club. (3) That the Association at its Annual Meeting shall decide the centre or centres overseas to be visited during the year. (4) That the Travelling Club shall be financially self-supporting and shall have no claim upon the general finances of the Association. (5) The Association to appoint annually a Secretary for the Travelling Club who shall be responsible for the detailed arrangements. Professor Tunbridge called attention to the words in Rule 1 of the Association, 'Its objects shall be the advancement of Internal Medicine and the promotion of friendship among Physicians', and to the financial difficulties now standing in the way of visits by physicians to the Continent. He pointed out that the senior members of the Association with established reputations are able to visit centres abroad without introductions and on a basis of personal friendship. The junior members, however, often feel diffident about imposing themselves on distinguished physicians, yet these junior members, and British medicine, would especially benefit from a greater opportunity for the interchange of ideas, experience, and friendship.

DR. E. R. CULLINAN spoke in favour of the proposal and formally seconded it. After some discussion by SIR HENRY TIDY and PROFESSOR L. J. WITTS, the President asked that a decision be deferred until after the next item had been taken.

PROFESSOR L. J. WITTS then spoke on the future of the Association. He referred to the Osler Centenary last year, with its reminder that the Association was now forty-three years old. Many of the original members had come to the end of their time, and there was a danger that the Association as a whole might become too senior, and that the impetus under which it was started might be lost. During these forty-three years there had been two world wars, and great changes in society and in medicine. He referred in particular to the multiplication of specialities and the great enlargement of the numbers of consultants, teachers, and researchers in internal medicine. First had come the specialist societies, beginning with the Cardiac Club, and now so numerous that there seemed no organ of the body without its own society. More recently, and particularly since the

Second World War, there had been the formation of international societies, both in internal medicine as a whole and in many specialized topics. Observation of these phenomena had provoked a number of questions. What was to be the position of the Association amongst this multiplicity of societies, and what was now the best way of achieving its objectives? Was the Association getting the best men and the best papers? Was membership of the Association of Physicians still regarded by the younger men as the blue ribbon of internal medicine in this country? One of the first suggestions for dealing with these problems was a medical week, when a number of the societies devoted to the study of internal medicine, in general or particular, would meet in the same place and at roughly the same time, as the Cardiac Club and the Association now met together. This suggestion had been considered by members of the Association and the specialist societies, and there was no doubt that the majority were against it. When a number of societies were gathered together, the meetings became too large and it was difficult to promote the fellowship which was one of the objects of the societies. There were similar objections to an enlargement in the membership of the Association. If the Association grew larger, it would not be possible to fit it into the average lecture-room or the average dining-hall, and the intimacy of the Association would be lost. A third possibility was to recognize that there were now too many general physicians for all to get into one Society. In the United States, for example, there were the Association of Physicians, the Society for Clinical Investigation or 'Young Turks', and the Federated Society or 'Young Young Turks'. In Great Britain many of the young active workers belonged to the Medical Research Society or its Scottish counterpart, the Scottish Society for Experimental Medicine. Today, therefore, it was not the same hardship for a physician to be outside the Association as it was in 1907, when there were no alternative societies. The danger, rather, was that the Association might be thought of as senescent and might lose its prestige. He did not think this ought to happen, as there was a kind of paper that belonged properly to the Association, in distinction from the research communications and specialized topics which were appropriate to other societies. The Association was interested in papers of clinical application and general significance. As examples, he would quote some of the papers given to the Association of American Physicians last year: the treatment of rheumatoid arthritis with ACTH and cortisone, the treatment of typhoid fever with chloramphenicol, the successful prophylaxis of syphilis with penicillin, and other topics of the same kind. He deplored the modern habit of picking things up by the roots to see how they were growing, and the blind faith in the advantages of co-ordination, integration, centralization, and rationalization. Nevertheless, he thought it might be wise for the Association to review its position and policy. The key questions seemed to him to be how large the Association should be, what should be the criteria for membership, and how they should maintain a consistent policy over the years. He therefore suggested that the President, with the Secretary and the Treasurer, should call together a small informal group, representative of both the older and the younger members of the Association, to discuss the topics he had mentioned. This group could report to the Executive Committee, and the Executive Committee could then, if it wished, make recommendations to the Association.

Sir Francis Fraser, in seconding the proposal, spoke of the position of the consultant not working in a teaching centre. Sir Henry Tidy agreed with the proposal of Professor Witts, and it was formally resolved that a small committee be set up to consider the future of the Association, to make recommendations, and to report to the Executive Committee.

On the invitation of the President, Professor Tunbridge agreed to withdraw his proposal that a Travelling Club be formed, pending the special Committee's Report.

SCIENTIFIC BUSINESS

Friday Morning, May 26

1. Dr. Russell Fraser, Dr. I. Doniach, and Dr. Q. J. Hobson (introduced) discussed *The Effect of Resorcinol as an Antithyroid Agent*. Dr. Fraser said that in the past winter, during a survey of the urinary excretion of I^{131} in cases of myxoedema, they had encountered three instances in which the myxoedema had been due to applying resorcin ointment to leg ulcers. Studies of the thyroid uptake and the protein-bound iodine of these patients before, during, and after reapplication of the ointment indicated that resorcinol interfered with the manufacture of thyroid hormone; the patients subsequently recovered spontaneously on withdrawing the ointment without any medication. All their cases had been characterized by a sudden onset of severe myxoedema, a goitre, and a leg ulcer to which resorcin had been applied for at least two years. By experiments on rats they had confirmed the fact that resorcin interfered with the thyroid uptake of iodine in a way comparable with the action of thiouracil. They also found that, among 66 in-patients diagnosed

in the previous 10 years as having spontaneous myxoedema, goitres were recorded in seven, three of these having Hashimoto's thyroiditis; and all the rest had leg ulcers and hyperplastic thyroids.

2. Dr. G. Watkinson (introduced by Professor R. E. Tunbridge) described his observations on changes of intragastric pH by the use of the 24-hour test meal. He reported the results of 140 24-hour test meals in 100 patients. He had found falls in acidity approximating to alkaline levels in half the 25 cases of gastric ulcer studied. Investigations into possible factors influencing nocturnal neutralization in gastric ulcer showed that variations in the site of the ulcer, and healing of the ulcer, might cause the fall in acidity to disappear. Owing to the variability of secretion he doubted the constancy of an individual secretory pattern. In 20 cases of histamine-fast achlorhydria he had shown that, although a true achlorhydria existed in association with anaemia, in dyspeptic achlorhydria he had often been able by this test to demonstrate abundant amounts of acid.

3. Dr. J. J. R. Duthie and Dr. B. Cruickshank (introduced by Professor L. S. P. Davidson) spoke on the *Relationship of Virus Hepatitis to Diffuse Hepatic Cirrhosis*. The communication was discussed by Professor H. P. Himsworth, Dr. J. B. Rennie, Professor G. W. Pickering, Professor J. W. McNee, and Professor R. Platt.

4. Dr. R. R. H. Lovell (introduced by Professor Pickering) described the *Structure of Clubbed Fingers*. He said that clinical and volumetric studies suggested that in clubbing associated with congenital heart disease, but not in that associated with other diseases, there was an increased blood-volume in the distal finger-segment. Examination of sections of fingers with blood-vessels fixed and stained in full dilatation had revealed the anatomical basis for this distinction, namely that conspicuous venous dilatation was present only in the congenital heart type of clubbing. He concluded that increased connective tissue, especially in the nail-bed, endowed a clubbed finger with its characteristic shape; the deformity was enhanced in congenital heart disease by dilatation of the cutaneous venous plexuses.

Dr. J. M. H. Campbell said that clinical evidence supported the importance of venous engorgement in clubbing of the fingers, for in some severe cases greatly distended veins might be seen extending back over the next phalanx or to the base of the finger, so massed that sometimes the whole finger might appear deep blue. This was not entirely a peripheral phenomenon, because distended veins were often visible over the chest. He thought that most cases of clubbing differed in degree rather than in type, and after many attempts he thought it best to classify them as slight, moderate, and severe; even in early cases, all the changes could be recognized. There were, however, certain older patients with much curvature of the nails but little broadening of the phalanx, and this seemed to occur where cyanosis had been present for a long time but was slight in degree, e.g. in some cases of Eisenmenger's complex.

Dr. Russell Fraser asked if Dr. Lovell had any evidence of the rate of growth of the nails in clubbed fingers.

Dr. R. W. Parnell mentioned a case, which had been under the care of Dr. W. E. Lloyd, of clubbing which affected individual fingers. A young woman, aged 22 years, had long-standing nephritis, hyperplasia of the parathyroids, and extensive metastatic calcification. There were large calcareous deposits in the hands and calcified digital arteries.

Dr. Lovell, in replying, said that the appearance of the nail in clubbing reflected earlier changes in the nail-bed, and its shape depended in part on the original form of the finger end. Finger-volume measurements showed rapid changes in clubbing when the associated disease was treated. The cause of the venous dilatation in congenital heart disease had not been determined. The peculiarly complex vascular arrangements in the distal finger-segment included large arteriovenous anastomoses, which might be of importance in the development of clubbing.

5. Dr. J. N. Cumings (introduced) and Professor E. A. Carmichael described their studies of calcium and phosphorus in patients with epilepsy and calcification of the basal ganglia.

The communication was discussed by Dr. E. H. Hudson and Dr. Russell Fraser.

The Association adjourned at 12.55 p.m. After lunch, members of the Association attended a clinical, pathological, and radiological demonstration at University College Hospital and Medical School, and also visited the Wellcome Museum of Medical Science,

where the Director, Dr. C. J. Hackett, demonstrated the Museum. At 3.45 p.m. the Association was entertained to tea in University College Hospital Medical School by the School Council.

4.45 p.m. Afternoon Session

6. Dr. E. G. L. Bywaters and Dr. A. S. Dixon (introduced) described *The Action of ACTH in Rheumatic Fever*. They had given pituitary adrenocorticotrophic hormone to eight children with rheumatic fever for eight days, and had noted a fall in temperature, pulse-rate, and sedimentation-rate, together with signs of adrenal stimulation. There had been no effect on the rash or the nodules, and in two cases pericardial friction had developed during treatment. The corrected QT interval had increased. They thought that the difference between these and the original American results was due to the different type of patient selected.

Dr. Paul Wood thought that the type of case chosen made it impossible to detect the effect, if any, of ACTH on active rheumatic carditis. He suggested that ACTH be given to patients as soon as a mitral or aortic diastolic murmur appeared. If this substance really influenced the rheumatic heart, these murmurs should disappear. Few patients would be statistically required for an answer to this question.

The President observed that it was very important to continue such research.

7. Dr. Oswald Savage (introduced by Dr. W. S. C. Copeman) described *The Effect of certain Steroid Substances in Cases of Rheumatoid Arthritis*. He had judged the therapeutic effect by selected pathological and biochemical tests, clinical function tests, detailed measurement of affected joints, and a standardized questionnaire. The substances had first been screened by a preliminary trial, followed, if indicated, by a longer controlled experiment which included the detailed metabolic study of at least one patient in each group. The substances he had employed were progesterone, pregnenolone, androsenedione, and dehydro-iso-androsterone in large dosage. Most of the results had proved clinically negative, but a severely crippled woman, aged 66 years, recovered dramatically after five days on progesterone. She ultimately relapsed, but it had been interesting to note that during the phase of improvement her urinary pregnanediol output fell to a very low level. When she relapsed clinically it returned to the expected level.

8. Dr. F. J. W. Miller (introduced by Professor Sir James Spence) described *Cases of Visible Primary Tuberculosis*. In three years he had seen 22 cases of primary infection of the eye, mouth, or skin. In each case there had been a small painless primary focus with rapid painless enlargement, to be followed by caseation of the regional lymph glands. In nine cases there had been a history of contact with an adult suffering from open tuberculosis. Untreated, the primary focus appeared to take about 18 months to heal, whereas there was rapid healing with streptomycin. He had also observed haematogenous spread from such foci, and one child had developed a tuberculous lesion in the right knee-joint, while another had developed a generalized miliary tuberculosis followed by fatal meningitis. He thought that primary infection in sites other than the lungs was more common than had hitherto been recognized.

9. Professor E. P. Sharpey-Schafer discussed *The Mechanism of 'Black-outs' in Superior Vena-caval Obstruction and after Violent Coughing*. The communication was discussed by Professor J. McMichael, Professor L. J. Witts, Dr. Hugh Barber, Dr. E. T. Freeman, Dr. W. Russell Brain, and Dr. D. Evan Bedford.

Annual Dinner

The Annual Dinner was held in the Grocers' Hall, Princes Street. The President, Sir John Parkinson, was in the Chair. The toast of the Association was proposed by the President. That of the guests was proposed by Dr. W. Russell Brain, and Dr. W. Logan, Principal of London University, replied. The toast of the President was proposed by Dr. D. Evan Bedford.

Saturday, 9.30 a.m. Morning Session

10. Dr. R. W. Parnell discussed the *Physical Type and Temperament of Undergraduates*. He had applied Sheldon's three-dimensional system of describing physique to standardized photographs of 184 undergraduates. The prevalence of psychosomatic signs found at routine health examination was examined according to the dominant dimension. He had found nail-biting, hay fever, dyspepsia, and nervous breakdown significantly more often in mesomorphs, but apprehensiveness at interview and nervous erythema more often in ectomorphs. The rise of endomorphy to secondary or, further, to primary dominance was

associated with less frequent psychosomatic signs. He quoted rates for suicide and nervous breakdown to show that disorders largely connected with temperament were of paramount importance among undergraduates.

11. Dr. Alice Stewart, Dr. Josefine Webb, and Dr. Ian Sutherland (introduced) discussed *The Spread of Tuberculosis between Neighbouring Households*. Dr. Webb described a statistical survey made in the Borough of Northampton to see whether there was any evidence of the spread of tuberculosis from an infected house to neighbouring houses. The investigation covered 28 years (1921–48) and fell into two parts. The first sought to determine whether there was more clustering of affected houses than would be expected by chance alone, and in the second part the time between the occurrence of cases in neighbouring houses had been studied. She considered that the findings showed there was a slight but definite tendency for the disease to spread from one house to that next door.

Dr. J. G. Scadding inquired whether the occupation of adjacent houses by related families had been investigated.

Dr. Stewart in reply stated that the family history in next-door houses had been carefully examined to see if infection in these houses could be traced to family relationships. Such relationship, however, was found to exist in one instance only.

12. Dr. Honor V. Smith (introduced by Professor W. Ritchie Russell) discussed *Some Effects of the Intrathecal Injection of Tuberculin*. She said that the effect of intrathecal injections of streptomycin on the cell- and protein-content of the cerebrospinal fluid in the treatment of tuberculous meningitis suggested that tuberculin might be liberated into the cerebrospinal fluid. In healthy subjects who were tuberculin-sensitive as shown by the Mantoux test, the intrathecal injection of minute amounts of the purified protein derivative of tuberculin (PPD) produced the disturbance in cell- and protein-content characteristic of tuberculous meningitis. Rather larger doses produced disturbances indistinguishable from those seen in tuberculous meningitis treated with intrathecal streptomycin. In subjects who were Mantoux-negative there was no significant disturbance. She had found that in patients with tuberculous meningitis intrathecal injections of PPD were of therapeutic value.

Dr. Neville Oswald suggested that perhaps the altered pathological reaction at the base of the brain might be accounted for by desensitization. It was well known that such desensitization could be rapidly produced in infected laboratory animals.

13. Dr. W. W. Payne (introduced by Professor A. A. Moncrieff) discussed *Infantile Renal Acidosis*. He had studied 22 cases of infantile renal acidosis since the end of 1946. In a typical case, after a few months of normal progress the infant ceased to gain weight, became apathetic and constipated, and lost his appetite; he refused solid or semi-solid foods, and vomited if the meal were forced; simple fluids were taken thirstily, and there was often polyuria; the respiration-rate was sometimes increased. The urine was usually alkaline, and might contain some white blood-cells and albumin, but there was never more than a transitory infection. Dehydration was frequent. The blood showed a raised chloride- and a lowered bicarbonate-level (chloride acidosis). The sodium varied, both high and low values being obtained. The potassium, calcium, and phosphorus showed no constant change, but the blood-urea was often raised. If untreated many of these infants died of inanition and intercurrent infection, but a proportion would spontaneously improve with careful nursing. He had found that treatment by large doses of alkalis quickly brought about symptomatic improvement and ultimately, after four to six months, the alkalis might be stopped without the acidosis recurring. In some cases X-ray evidence suggestive of calcification of the renal medulla was found, linking the condition with the adult 'nephrocalcinosis with hyperchloraemia'. He considered that the underlying cause was a renal tubular defect, possibly delayed maturation of function.

Professor A. A. Moncrieff said that there was a considerable number of unrecognized cases in this country.

Dr. B. E. Schlesinger asked if any particular type of patient was affected.

Dr. C. L. Cope wondered if hyperventilation was of any diagnostic value in this condition.

Dr. D. A. K. Black asked whether Dr. Payne had observed any changes in the plasma-electrolytes of normal infants which would suggest that their acid-base regulation was under strain, even if they did not show the complete syndrome of renal acidosis.

Dr. Russell Fraser asked if there were any illness preceding the symptoms of acidosis which might have precipitated this disease.

In reply DR. PAYNE said that it had not been noticed that any particular type of patient was affected. Hyperventilation was seen sometimes, and was of considerable diagnostic value when present. He had made no observation of completely normal infants, but observation of infants suffering from gastro-enteritis had showed that their acid-base regulation was very easily disturbed, and could mimic temporarily the changes found in renal acidosis. The history was usually rather a long one, and intercurrent illnesses might occur, but there was no suggestion of any actual illness precipitating the onset of the condition.

14. DR. W. H. H. ANDREWS (introduced) and PROFESSOR B. G. MAEGRAITH discussed *Recent Work on Circulation in the Liver, and its Significance in the Pathogenesis of Liver Disease*. Dr. Andrews said that hepatic centrilobular necrosis was probably due to anoxia brought about by generalized and localized factors. Local factors were generally vascular. In this study of the blood-vessels of the liver they had observed a network of large sinusoids which surrounded the portal tracts. Blood from the portal vein, from the hepatic artery, and from vessels surrounding the bile-duct ran into this network, and thence to the sinusoids of the lobule. Dr. Andrews said that hepatic anoxia in dogs and other animals, in anaphylaxis, was produced by a slowing of the blood in the hepatic venous tree. There was evidence that this slowing occurred in other forms of shock, and might occur in man.

DR. F. G. LESCHER said that he had been interested in the progress of liver-function tests in early cases of neurosyphilis treated with malaria and penicillin. In a number of cases liver function became normal, or was better than before treatment.

15. DR. M. H. ROSCOE (introduced by PROFESSOR R. PLATT) discussed *Anaemia in Renal Disease*. She said that the anaemia was normochromic in all the conditions investigated. In acute Type 1 nephritis there was blood dilution, producing an apparent anaemia, but this disappeared when, with diuresis, the blood-volume returned to normal. A true anaemia developed at the same time, and became noticeable if recovery was delayed. In early Type 2 nephritis there was no anaemia, but it occurred with prolonged hypoproteinaemia and was proportional to the serum-albumin level. In forms of renal disease with nitrogen-retention anaemia developed as the blood-urea rose.

PROFESSOR PLATT said that the haemodilution of acute Type 1 nephritis, which had been so clearly demonstrated by the speaker and had been found by others, finally disposed of the theory of increased capillary permeability as a cause of the oedema of acute nephritis. If oedema were due to increased capillary permeability, fluids should leave the vessels and haemoconcentration should result. Haemodilution suggested that the oedema was due to retention of salt and water by the kidney.

PROFESSOR J. MCMICHAEL said that similar changes in blood volume and haemoconcentration might accompany recovery from congestive heart failure. The venous pressure was nearly always raised in the acute stage of Type 1 nephritis, falling with recovery. It would be equally possible, therefore, to ascribe the results observed to recovery from the circulatory complications of acute nephritis.

PROFESSOR L. J. WITTS reported that Loge, in Carl Moore's department in St. Louis, had been studying the anaemia of advanced nephritis, using the Ashby technique for red-blood-cell survival and the uptake of radioactive iron for red-blood-cell manufacture. He had found that there was both diminished formation and increased breakdown of blood, and wondered whether these things could be due to an excess of phenols in the plasma.

In reply DR. ROSCOE said that the true anaemia of acute Type 1 nephritis was probably similar to that of infection, and its aetiology was as obscure.

16. DR. C. M. FLETCHER and DR. J. C. GILSON (introduced) described *A Comparison of the Clinical and Physiological Assessments of Emphysema*. Dr. Fletcher said that an attempt had been made to measure numerically certain physical signs which were commonly regarded as indicating emphysema, in 50 normal men and miners with pneumoconiosis, and in four cases of clinical emphysema in non-miners, between the ages of 50 and 60 years. The numerical assessment thus reached had been found to bear little relation to vital capacity, maximum breathing capacity, or to the Bates-Christie index of emphysema, but it had been more closely related to the residual air expressed as a percentage of the total lung-volume, and also to the volume of gas required for complete gas replacement in the lungs. He therefore considered that the physical signs and certain respiratory function tests were largely measuring the same thing, but whether this thing were emphysema remained in doubt. He suggested that progress might be made by defining clinical and physiological syndromes, to one of which the term 'emphysema' might, by agreement, become attached.

PROFESSOR R. V. CHRISTIE pointed out that Dr. Fletcher in his opening remarks had mentioned the difficulties involved in the early diagnosis of emphysema; he would go further in saying that he was not at all happy about the criteria Dr. Fletcher had used. The signs he had recorded, with the exception of faint breath sounds, belonged to what Cabot had called the barrel-chest phenomenon, and it had been repeatedly shown that this might bear no relation to the symptoms of emphysema or to the presence of emphysema as found at autopsy. In a group of silicotics such as Dr. Fletcher had investigated he did not believe it was possible to diagnose emphysema in any but its later stages.

DR. D. V. BATES (introduced) said there was an additional piece of evidence which supported the comment that Professor Christie had made. It was not difficult to find persons in whom there could be no clinical suspicion of the presence of emphysema, but in whom the residual air index mentioned by Dr. Fletcher was raised to the level of that found in emphysema. There was some evidence that this raised index was due to a change in the position of the thoracic cage, and this would support the belief that the correlation Dr. Fletcher had found was a correlation between the barrel-chest phenomenon and the residual-air index, and not due to emphysema.

DR. J. L. LIVINGSTONE asked if bronchospasm was a frequent accompaniment of emphysema in miners, and, if so, had Dr. Fletcher tried the effect of adrenaline in estimating the respiratory function. The measurement of the time taken to complete expiration was a useful gauge of the degree of emphysema and bronchospasm. If this time were reduced after adrenaline, it would give an idea as to the degree of bronchospasm present in addition to the actual emphysema.

DR. C. L. COPE asked, since Dr. Fletcher had been unable to find a satisfactory definition of emphysema, and yet Professor Christie recommended that 'pure' cases be studied, what would be the definition of 'pure' emphysema proposed by Professor Christie which would be acceptable to Dr. Fletcher?

DR. FLETCHER in his reply suggested that emphysema, like other diseases, might exist without symptoms. Bronchial spasm, he added, was nearly always found in advanced cases of pneumoconiosis.

On Saturday afternoon a party of members and their wives travelled by steamer to the Royal Naval College, Greenwich. They made a tour of the College, and after tea visited the National Maritime Museum.

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